risperidone - Drug Summary

Jump to Section

CLASSES
BOXED WARNING
DEA CLASS
DESCRIPTION
COMMON BRAND NAMES
View All Sections...

Related Drug Information

CLASSES

Serotonin-Dopamine Antagonist (SDA) Antipsychotics

BOXED WARNING

Dementia, geriatric, stroke

Lower initial doses of risperidone are recommended in geriatric patients due to decreased medication clearance in this population and a greater frequency of hepatic, renal and cardiac dysfunction, concomitant chronic disease, and other drug therapy. To decrease the incidence of orthostatic hypotension, careful titration of risperidone dosage is recommended. Antipsychotics, like risperidone, are not approved for the treatment of dementia-related psychosis in geriatric patients. In April 2005 the FDA mandated that all manufacturers of atypical antipsychotics include a boxed warning to the labeling indicating that increased death rates (1.6 to 1.7 times that of placebo) have been noted in this patient population receiving atypical antipsychotics. Death typically occurred due to heart failure, sudden death, or infections (primarily pneumonia). Of 17 placebo controlled trials (n = 5,106) performed with olanzapine, aripiprazole, risperidone, or quetiapine in elderly patients with dementia-related psychosis, 15 showed numerical increases in mortality in the active compared to the placebo-treated patients. In June 2008, FDA required manufacturers of conventional antipsychotics to also add a boxed warning to their product labeling regarding an increased risk of death in elderly patients with dementia. A significantly increased incidence of cerebrovascular events (stroke, transient ischemia attack) have been reported in the elderly with dementia-related psychosis taking risperidone vs. placebo (n = 1,230). Some events have been fatal; use risperidone with extreme caution in elderly patients with cerebrovascular disease. Patients with Dementia with Lewy Bodies are thought to experience an increased sensitivity to antipsychotics manifest as confusion, obtundation, postural instability with frequent falls, extrapyramidal effects, and symptoms resembling neuroleptic malignant syndrome. According to the Beers Criteria, antipsychotics are considered potentially inappropriate medications (PIMs) in elderly patients, and use should be avoided except for treating schizophrenia or bipolar disorder, and for short-term use as antiemetics during chemotherapy. In addition, avoidance of risperidone is recommended in geriatric patients with the following disease states or symptoms due to the potential for exacerbation of the condition or increased risk of adverse effects: Parkinson's disease (symptom exacerbation), delirium (possible new-onset or worsening delirium), and dementia (adverse CNS effects). There is an increased risk of stroke and greater rate of cognitive decline and mortality in persons with dementia receiving antipsychotics, and the Beers expert panel recommends avoiding antipsychotics to treat delirium- or dementia-related behavioral problems unless non-pharmacological options have failed or are not possible and the patient is a substantial threat to self or others. The Panel recommends avoiding antipsychotics in elderly patients with a history of falls or fractures, unless safer alternatives are not available, since antipsychotics can cause ataxia, impaired psychomotor function, syncope, and additional falls; if an antipsychotic must be used, consider reducing use of other CNS-active medications that increase the risk of falls and fractures and implement other strategies to reduce fall risk. Because antipsychotics can cause or exacerbate hyponatremia and SIADH and the elderly are at increased risk of developing these conditions, sodium levels should be closely monitored when starting or changing dosages of antipsychotics in older adults. The federal Omnibus Budget Reconciliation Act (OBRA) regulates medication use in residents of long-term care facilities (LTCFs). An antipsychotic should generally be used only for the conditions listed in the guidelines (e.g., schizophrenia, mood disorder, Tourette's disorder) and that meet the Diagnostic and Statistical Manual of

Mental Disorders (DSM) criteria for use. There is an increased risk of morbidity and mortality in elderly patients treated with antipsychotics for dementia-related psychosis. Therefore, identify and address all possible causes of behavioral or psychological symptoms of dementia (BPSD) before considering an antipsychotic. To initiate antipsychotic therapy, behavioral symptoms must be a danger to self or others and are either 1) due to mania or psychosis or 2) the plan of care includes documentation of attempted behavioral interventions (except in an emergency). Limit emergency treatment to 7 days or less with evaluation and documentation within 7 days which identifies and addresses contributors/causes. For acute conditions persisting beyond 7 days, pertinent non-pharmacologic interventions must be attempted, unless clinically contraindicated, and documented. Treatment of non-acute, chronic, or prolonged BPSD must meet all of the OBRA criteria for BPSD treatment, and include monitoring that ensures the behavioral symptoms are not due to a treatable or correctable medical condition, are not due to correctable environmental or treatable psychological stressors alone, and provides clearly documented evidence of persistence. The LTCF must evaluate the appropriateness of the antipsychotic during or within 2 weeks of admission for a newly admitted resident on an antipsychotic. In all cases, the lowest possible dose and shortest duration should be prescribed. OBRA provides general dosing guidance for antipsychotic treatment of BPSD. Monitoring of antipsychotics should include evaluation of ongoing effectiveness, rationale for use, and potential adverse effects (e.g., anticholinergic effects, neurological symptoms, metabolic syndrome, cardiac effects). Antipsychotics are subject to periodic review for effectiveness, necessity, and the potential for gradual dose reduction (GDR) or discontinuation. Refer to the OBRA guidelines for complete information.

DEA CLASS

Rx

DESCRIPTION

Oral and depot intramuscular atypical antipsychotic
FDA approved in adults for positive and negative symptoms of schizophrenia and for bipolar I disorder; only approved in adults for depot IM use
In selected pediatric patients, approved for treatment of schizophrenia, bipolar I disorder, and irritability associated with autistic disorder
As with all antipsychotics, increased mortality risk in elderly patients treated for dementia-related psychosis

COMMON BRAND NAMES

Risperdal, Risperdal Consta, Risperdal M-Tab

HOW SUPPLIED

Risperdal Consta Intramuscular Inj Pwd F/Sol: 12.5mg, 25mg, 37.5mg, 50mg
Risperdal M-Tab/Risperidone Oral Tab Orally Dis: 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg
Risperdal/Risperidone Oral Sol: 1mg, 1mL
Risperdal/Risperidone Oral Tab: 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg

DOSAGE & INDICATIONS

For the treatment of schizophrenia.

Oral dosage

Adults

To minimize the risk for orthostatic hypotension and syncope, initiate at 2 mg/day PO given as a single dose or as 1 mg PO twice per day. Adjust dose at intervals of at least 24 hours and in increments of 1 mg/day to 2 mg/day as tolerated to the recommended target dose of 4 mg/day to 8 mg/day PO. Effective range: 4 mg/day to 16 mg/day PO. The total daily dose of risperidone may be administered once daily or in 2 divided doses. During clinical trial evaluation, doses above 6 mg/day PO were not more effective than lower doses and they were associated with more extrapyramidal symptoms and other adverse effects. In one study, the efficacy results for 8 mg/day were generally greater than for 4 mg/day. Patient response to antipsychotics is variable. Individualize dosage. Use the lowest effective dose. Max: 16 mg/day PO. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. A dose reduction should be considered if hypotension occurs. Maintenance treatment is typically recommended for patients who have responded to initial treatment. Periodically re-assess the need for continued treatment. In one controlled trial, doses of 2 mg/day to 8 mg/day effectively delayed relapse in adult patients who had been clinically stable for at least 4 weeks and were then followed for 1 to 2 years. RE-INITIATION OF TREATMENT: The initial dose titration should be followed in patients who have previously discontinued the drug.

Geriatric Adults

To minimize the risk of orthostatic hypotension and syncope, initiate with 0.5 mg PO twice per day followed by careful titration. The usual adult titration schedule includes dose adjustments at intervals of at least 24 hours and in increments of 1 mg/day to 2 mg/day as tolerated to the recommended target dose range of 4 mg/day to 8 mg/day PO. Slower titration may be needed in geriatrics due to the potential for impaired renal function. Effective dose range: 4 mg/day to 16 mg/day PO. May give the total daily dose once daily or in 2 divided doses. During clinical trial evaluation, doses above 6 mg/day were not more effective than lower doses and were associated with more extrapyramidal symptoms and other

adverse effects. Individualize dosage. Use the lowest effective dose. Max: 16 mg/day PO. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. A dose reduction should be considered if hypotension occurs. Maintenance treatment is typically recommended for patients who have responded to initial treatment. Periodically re-assess the need for continued treatment. RE-INITIATION OF TREATMENT: The initial dose titration should be followed in patients who have previously discontinued the drug.

Adolescents

0.5 mg PO once daily initially. May administer in divided doses to increase tolerability. Adjust dose at intervals of at least 24 hours and in increments of 0.5 to 1 mg/day as tolerated to the recommended target dose of 3 mg/day. The effective dose range is 1 to 6 mg/day PO; however, doses above 3 mg/day do not appear to provide additional therapeutic benefits and may result in more adverse events. Max: 6 mg/day PO. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. Responding patients generally continue treatment beyond the acute episode. Periodically reassess safety and efficacy during chronic use.

Children† 8 to 12 years

Dosage not established; not FDA-approved. 0.5 mg/day PO initially. May give in divided doses to increase tolerability. Follow with gradual titration based on response and tolerability. Max: 6 mg/day PO. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. In one randomized, controlled trial of pediatric patients with early-onset schizophrenia, schizoaffective disorder, or schizophreniform disorder, children 8 to 11 years received 0.5 mg/day PO on Day 1, with an increase to 1 mg/day on Day 6, 1.5 mg/day on Day 11, and 2 mg/day on Day 15 as clinically indicated; thereafter, gradual titration occurred as needed in increments of 1 mg/day up to a maximum of 6 mg/day. Children 12 years received 0.5 mg/day on Day 1, with titration up to 3 mg/day by Day 11, and titration thereafter as clinically indicated in increments of 1 mg/day up to a maximum of 6 mg/day.

Intramuscular depot dosage (Risperdal Consta)

Adults

Usual dose: 25 mg IM (deep gluteal or deltoid injection) once every 2 weeks. Doses above 25 mg IM every 2 weeks do not appear to provide greater efficacy; however, some adult patients not responding to the 25 mg dose may benefit from 37.5 mg or 50 mg IM once every 2 weeks. Titrate dose no more frequently than every 4 weeks; clinical effects from dosage titration may not be evident for 3 weeks. Oral risperidone (or other antipsychotic) should be initiated and continued for 3 weeks after the first depot injection to ensure that adequate plasma concentrations of depot risperidone are attained prior to discontinuation of the previous therapy. In patients who have never received risperidone, establish tolerability before initiating IM; when reinitiating IM treatment, supplement with the oral dose for 3 weeks. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. GERIATRIC PATIENTS: The recommended dose is 25 mg IM once every 2 weeks. During clinical trial evaluation, no differences in tolerability were observed between otherwise healthy geriatric versus younger adult patients. Therefore, dosing recommendations for otherwise healthy elderly patients are the same as for younger adults. However, instructions on preventative measures for orthostasis should be provided. Monitoring of orthostatic vital signs should be considered in elderly patients for whom orthostatic hypotension is a concern. OTHER DOSE ADJUSTMENTS: Initiation with 12.5 mg IM may be appropriate in those with renal or hepatic impairment, during concurrent use of medications which increase risperidone plasma levels, and in those with a history of poor tolerability to the drug.

For the treatment of bipolar disorder (Bipolar I Disorder), including acute mania or mixed episodes and maintenance therapy.

For the treatment of acute mania or mixed episodes associated with Bipolar I Disorder.

Oral dosage

Adults

Initially, 2 mg/day to 3 mg/day PO once daily as monotherapy or as an adjunct to lithium or valproate. If needed, adjust the dose by 1 mg/day at intervals of no less than 24 hours. A dose range of 1 mg/day to 6 mg/day PO was evaluated and found effective in clinical trials; higher doses were not studied. Individualize according to response and tolerability. Slower titration or divided daily doses may be needed in some patients. Use the lowest effective dosage. Efficacy of risperidone as monotherapy for manic episodes was demonstrated in two 3-week, randomized, controlled trials. The mean modal dose ranged from 4.1 mg/day to 5.6 mg/day. Results from one study indicate that risperidone 6 mg has equivalent efficacy to lithium (800 mg/day to 1200 mg/day) and haloperidol (10 mg/day) in the monotherapy treatment of acute mania. In a 3-week, double-blind controlled trial, risperidone plus a mood stabilizer (i.e., lithium or divalproex) was shown to be more efficacious than a mood stabilizer alone and as efficacious as haloperidol plus a mood stabilizer for the rapid control of manic symptoms as assessed by the Young Mania Rating Scale (YMRS). Further significant reductions in the YMRS were seen during the 10-week, open-label extension phase of treatment with risperidone plus a mood stabilizer. Concerns about extrapyramidal symptoms have been noted in bipolar clinical trials; lower doses in bipolar disorder (vs. schizophrenia) should be considered. In general, pharmacological treatment is continued beyond acute stabilization; however, there are no systematically obtained data to support the use of risperidone beyond 3 weeks. Periodically re-assess the need for continued treatment. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions.

Geriatric Adults

Initially, 0.5 mg PO twice per day followed by careful titration. If needed, adjust the dose by 1 mg/day at intervals of no less than 24 hours. Slower titration or divided doses may be needed in geriatric patients due to the potential for impaired renal function and an increase in drug toxicity. A dose range of 1 mg/day to 6 mg/day PO was evaluated and found effective in clinical trials in younger adults; higher doses were not studied. Individualize according to response and tolerability. Use the lowest effective dosage. Efficacy of risperidone as monotherapy or along with a mood stabilizer (i.e., lithium or divalproex) has been noted in trials for acute mania. Further significant reductions in the YMRS were seen during the 10-week, open-label extension phase of treatment with risperidone plus a mood stabilizer. Concerns about extrapyramidal symptoms have been noted in bipolar clinical trials; lower doses in bipolar disorder (vs. schizophrenia) should be considered. In general, pharmacological treatment is continued beyond acute stabilization; however, there are no systematically obtained data to support the use of risperidone beyond 3 weeks. Periodically re-assess the need for continued treatment. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions.

Children and Adolescents 10 to 17 years

Initially, 0.5 mg PO once daily in the morning or evening as monotherapy. May administer in divided doses to increase tolerability. Adjust dose at intervals of at least 24 hours and in increments of 0.5 mg/day to 1 mg/day as tolerated to the recommended target dose range of 1 mg/day to 2.5 mg/day PO. Doses above 2.5 mg/day do not appear to provide additional therapeutic benefits and may result in more adverse events. Doses above 6 mg/day PO have not been studied. Safety and efficacy of risperidone as an adjunct treatment to lithium or valproate in pediatric patients have not been established. Safety and efficacy of the drug beyond 3 weeks in adolescents have not been systematically evaluated. Individualize dose according to response and tolerability. Use the lowest effective dosage. In general, pharmacological treatment is continued beyond acute stabilization; however, there are no systematically obtained data to support the use of risperidone in longer-term treatment (i.e., beyond 3 weeks). Periodically re-assess the need for continued treatment. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions.

For the maintenance treatment of Bipolar I Disorder as monotherapy or adjunct therapy to lithium or valproate.

Intramuscular depot dosage (i.e., Risperdal Consta)

Adults

Establish tolerability with oral risperidone prior to converting to IM extended-release risperidone (Risperdal Consta) in patients who have never received risperidone. Then initiate Risperdal Consta with 25 mg IM every 2 weeks. Oral risperidone (or another antipsychotic) should be given with the first injection of Risperdal Consta, and continued for 3 weeks to ensure adequate therapeutic plasma concentrations from Risperdal Consta. Some patients may benefit from doses of 37.5 mg to 50 mg IM every 2 weeks. Upward dose adjustments should not be made more frequently than every 4 weeks. Dosages above 50 mg every 2 weeks have not been studied in this patient population. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. GERIATRIC PATIENTS: The recommended dose for geriatric patients is 25 mg IM once every 2 weeks. During clinical trial evaluation, no differences in tolerability were observed between otherwise healthy geriatric versus younger adult patients. Therefore, dosing recommendations for otherwise healthy elderly patients are the same as for younger adults. However, because elderly patients have a greater tendency towards orthostatic hypotension, instructions on preventative measures for orthostasis should be provided. Monitoring of orthostatic vital signs should be considered in elderly patients for whom orthostatic hypotension is a concern. OTHER DOSE ADJUSTMENTS: A lower initial dose of 12.5 mg may be appropriate for those with renal impairment, hepatic impairment, a history of poor tolerability to psychotropic medications, or regimens with the potential for drug interactions with risperidone. It should be noted that efficacy of the 12.5 mg dose has not been established. Re-evaluate the need for continued treatment during long-term use.

For the treatment of irritability associated with autistic disorder.

Oral dosage

Children and Adolescents 5 to 17 years and weighing 20 kg or more

0.5 mg PO once daily, initially, for at least 4 days. Then may increase to recommended dose of 1 mg PO daily. May administer in divided doses to increase tolerability. Maintain this dose for at least 14 days. Thereafter, adjust as clinically necessary at intervals of at least 2 weeks and increments of 0.5 mg/day PO. Effective dose range: 0.5 mg to 3 mg/day PO. Safety and efficacy should be periodically re-assessed during long-term treatment. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions.

Children and Adolescents 5 to 17 years and weighing 15 to 19 kg

0.25 mg PO once daily, initially, for at least 4 days. Then may increase to recommended dose of 0.5 mg PO daily. May administer in divided doses to increase tolerability. Maintain this dose for at least 14 days. Thereafter, adjust as clinically necessary at intervals of at least 2 weeks and increments of 0.25 mg/day PO. Effective dose range is 0.5 mg to 3 mg/day PO. Safety and efficacy should be periodically re-assessed during long-term treatment. Coadministration of certain drugs may need to be avoided or

dosage adjustments may be necessary; review drug interactions.

For the treatment of moderate to severe tics associated with Tourette's syndrome†.

Oral dosage

Adults

Use low doses (e.g., 0.5 mg/day PO) initially with titration up to 6 mg/day PO based on response and tolerability. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. Results from small randomized studies suggest that the average effective dose is approximately 2.5 mg/day to 4 mg/day. In one study of 50 patients ranging from 11 to 50 years of age, a mean risperidone dose of 3.8 mg/day (range: 0.5 mg/day to 6 mg/day) was similar in efficacy to a mean pimozide dose of 2.9 mg/day. In a separate study of 46 patients between 14 and 49 years of age, significantly more patients responded to risperidone at a median dose of 2.5 mg/day (range: 1 mg/day to 6 mg/day PO) than placebo on the Global Severity Rating of the Tourette Syndrome Severity Scale (60.8% vs. 26.1% response rate). Risperidone was superior to placebo in improving tic severity (32% vs. 7%) in a short-term study enrolling 34 pediatric and adult subjects (8 adults up to 62 years of age) at a mean daily risperidone dose of 2.5 mg/day. Further evaluation in adult populations alone is necessary to more clearly establish the effective dose.

Children and Adolescents 7 to 17 years

Low initial doses are suggested (e.g., 0.25 mg/day to 0.5 mg/day PO); the usual effective dose range is 1 mg/day to 4 mg/day PO. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. One small study of children and adolescents 7 years of age and older used a maximum of 4 mg/day after titration; the mean effective dose was 2.5 mg/day PO. A separate study that included adolescents 14 years of age and older used a maximum of 6 mg/day PO; a median dose of 2.5 mg/day (range 1 mg/day to 6 mg/day) was superior to placebo ($p < 0.05$).

For the treatment of moderate to severe disruptive behaviors† (e.g., aggression) associated with oppositional defiant disorder† or other disruptive behavioral disorders†.

Oral dosage

Adolescents

In one study, body weight was used to determine dosage. Those weighing less than 50 kg received 0.25 mg/day PO initially; if weight 50 kg or more, 0.5 mg/day PO was given initially. Thereafter, the dose was increased gradually by 0.25 mg for patients less than 50 kg or 0.50 mg for those weighing 50 kg or more to a maximum daily dose of 0.75 mg/day PO for patients less than 50 kg or 1.5 mg/day PO for those 50 kg or more. The mean risperidone dosage was approximately 0.02 mg/kg/day.] Doses have varied among studies. In a comprehensive review, the mean risperidone dose ranged from 0.98 to 1.5 mg/day at study end for all studies evaluated. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions.

Children 5 to 12 years

0.01 mg/kg/day PO for at least 2 days is a suggested initial weight-based dose. Then, may titrate to 0.02 mg/kg/day for 5 days, and subsequently adjust weekly as clinically indicated by 0.02 mg/kg/day. Max: 0.06 mg/kg/day PO. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. In one study, body weight was used to determine dosage. Those weighing less than 50 kg received 0.25 mg/day PO initially; if weight was 50 kg or more, 0.5 mg/day PO was given initially. Thereafter, the dose was increased gradually by 0.25 mg for patients less than 50 kg or 0.5 mg for those weighing 50 kg or more to a maximum daily dose of 0.75 mg/day PO for patients less than 50 kg or 1.5 mg/day PO for those 50 kg or more. The mean risperidone dosage was approximately 0.02 mg/kg/day.] Doses have varied among studies, with mean risperidone doses ranging from 0.98 to 1.7 mg/day at the end of the studies. In a double-blind, placebo-controlled study of 110 children with a disruptive behavior disorder (DBD) and subaverage IQ, the decline in symptom ratings was 47.3% in the risperidone group vs. 20.9% in the placebo group. At study end, 25% of children in the placebo group were rated by the investigator as improved to some degree compared to 77% of children in the risperidone group. Some data have demonstrated sustained long-term improvement. In a 9-week randomized trial of 168 children (age: 6 to 12 years) with attention-deficit/hyperactivity disorder (ADHD) and a DBD (ODD or conduct disorder), the addition of risperidone to a psychostimulant and parent training showed significant improvements in measures of aggression and serious behavioral problems compared to those receiving stimulant and parent training only. Risperidone therapy (mean dose: 1.7 +/- 0.75 mg/day) was added at weeks 4 to 6 only if there was a need for improvement. For children weighing less than 25 kg, risperidone 0.5 to 2.5 mg/day was given; for children 25 kg or more, doses ranged from 0.5 to 3.5 mg/day. In a post-hoc analysis of children with ADHD and a DBD, risperidone-treated children had clinically and statistically significant reductions in disruptive behavior and hyperactivity subscale scores compared to placebo, regardless of concomitant stimulant use. However, further study is needed on the use of risperidone in the treatment of ADHD. Efficacy in children with ADHD alone or in long term settings has not been established, and the drug is not without adverse effects.

For the treatment of delirium† in the pediatric intensive care unit (PICU).

Oral dosage

Children and Adolescents

Limited data available, particularly in young children. Maintenance doses ranging from 0.2 to 2 mg/day

PO have been reported as efficacious with no adverse events noted (n = 30; age range: 4 months to 17 years). One small case series (n = 11; age range: 4 months to 16 years) used a loading dose of 0.1 to 0.2 mg PO. Begin at the lower end of the dosing range for younger, smaller patients. A mode individual dose of 0.5 mg has been reported in a small case series of older children and adolescents (n = 6; age range: 5 to 15 years). Some experts have suggested 0.5 to 2.5 mg/day PO given in 2 to 4 divided doses for patients 5 to 16 years of age. Max dosing is based on weight: less than 20 kg = 1 mg/day; 20 to 45 kg = 2.5 mg/day; more than 45 kg = 3 mg/day. In a review of data from 110 seriously-ill patients with delirium who were treated with atypical antipsychotics, a limited number of the same or lower doses were used as needed to control persistent symptoms and a routine daily dose was established based on the total amount needed to gain control of symptoms. Of those receiving risperidone (n = 13; mean age: 8.6 years; range: 1 to 16 years), a mean starting dose of 0.6 mg/day (range: 0.25 to 1 mg/day), mean ending dose of 0.7 mg/day (range: 0.25 to 2 mg/day), mean maximum dose of 1 mg/day (range: 0.25 to 2 mg/day), and average dose of 1.3 mg/day (range: 0.375 to 4 mg/day) was used. Antipsychotic was discontinued as soon as possible; mean length of therapy was 17.5 days (range: 2 to 54 days). Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions.

For the treatment of severe behavioral or psychological symptoms of dementia†.

Oral dosage

Geriatric Adults

If treatment is deemed necessary, 0.25 mg PO once or twice daily is a common initial dose. Based on study findings, risperidone 1 mg/day to 2 mg/day PO, given in divided doses, is more efficacious than placebo in improving dementia-related behavioral symptoms, especially psychosis and aggression. Suggested Max: 2 mg/day PO. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions. According the Agency for Healthcare Research and Quality efficacy review, risperidone is efficacious as treatment for behavioral symptoms of dementia. Risperidone is the only atypical antipsychotic with moderate to high quality in strength of evidence in efficacy of all 3 dementia categories reviewed: dementia-overall behavioral symptoms, dementia-psychosis symptoms, and dementia-agitation symptoms. Antipsychotics are not FDA-approved for this indication and the labeling of all antipsychotics contains a boxed warning noting an increased risk of death in geriatric patients being treated for behavioral problems associated with dementia. The federal Omnibus Budget Reconciliation Act (OBRA) regulates the use of antipsychotics in long-term care facility (LTCF) residents with dementia-related behavioral symptoms. OBRA Max: 2 mg/day PO in residents meeting the OBRA criteria for treatment, except when documentation is provided showing that higher doses are necessary to maintain or improve the resident's functional status. In addition, the facility must attempt a gradual dose reduction (GDR) in 2 separate quarters, at least 1 month apart, within the first year of admission to the facility or after the facility has initiated an antipsychotic, unless clinically contraindicated. After the first year, a GDR must be attempted annually unless clinically contraindicated. The GDR may be considered clinically contraindicated if the target symptoms returned or worsened after the most recent GDR attempt within the facility and the physician has documented justification for why attempting additional dose reductions at that time would likely impair the resident's function or increase distressed behavior.

†Indicates off-label use

MAXIMUM DOSAGE

Adults

16 mg/day PO for schizophrenia; 6 mg/day PO for bipolar disorder; 50 mg depot IM every 2 weeks for schizophrenia or bipolar disorder.

Geriatric

16 mg/day PO for schizophrenia; 6 mg/day PO for bipolar disorder; 50 mg depot IM every 2 weeks for schizophrenia or bipolar disorder.

Adolescents

6 mg/day PO for schizophrenia or bipolar I disorder; 3 mg/day PO for autistic disorder; 0.06 mg/kg/day PO has been suggested for the treatment of tics or severe behavior disorders associated with Tourette's or ADHD; safety and efficacy of injectable administration is not established.

Children

10 to 12 years: 6 mg/day PO for bipolar I disorder; 3 mg/day PO for autistic disorder but not FDA approved for autistic disorder in patients weighing less than 15 kg; 0.06 mg/kg/day PO has been suggested in developmental disability with severe disruptive behaviors; not FDA approved for schizophrenia; safety and efficacy of injectable administration is not established.
5 to 9 years: 3 mg/day PO for autistic disorder but not FDA approved for autistic disorder in patients weighing less than 15 kg; 0.06 mg/kg/day PO has been suggested in developmental disability with severe disruptive behaviors; not FDA approved for bipolar disorder or schizophrenia; safety and efficacy of injectable administration is not established.
Less than 5 years: Safety and efficacy have not been established.

Infants

Not indicated.

Neonates

Not indicated.

DOSING CONSIDERATIONS

Hepatic Impairment

Oral formulations: In adult patients with a Child Pugh score of 10 to 15, the recommended initial starting dose is 0.5 mg PO twice daily; titrate in increments of 0.5 mg or less. For doses more than 1.5 mg PO twice daily, titrate in weekly intervals. Specific guidelines for pediatric patients are not available.

Patients with hepatic impairment receiving the intramuscular depot injection: Adult patients with hepatic impairment should be treated with titrated doses of oral risperidone prior to initiating treatment with IM depot risperidone. In adults, the recommended oral titration starting dose is 0.5 mg PO twice a day during week one; increase to 1 mg PO twice a day or 2 mg PO once daily during week two. If a daily dose of at least 2 mg is well tolerated, 25 mg IM every 2 weeks may be started; higher dosages are not recommended. Continue oral risperidone for 3 weeks after the first depot injection, then discontinue. A slower titration beginning with 12.5 mg IM may be more appropriate for some patients. Efficacy of the 12.5 mg dose has not been evaluated in clinical trials.

Renal Impairment

Oral formulations: In adult patients with a CrCl less than 30 mL/minute, the recommended initial starting dose is 0.5 mg PO twice daily; titrate in increments of 0.5 mg or less. For doses more than 1.5 mg PO twice daily, titrate in weekly intervals. Specific guidelines for pediatric patients are not available.

Patients with renal impairment receiving the intramuscular depot injection: Adult patients with renal impairment should be treated with titrated doses of oral risperidone prior to initiating treatment with IM depot risperidone. In adults, the recommended oral titration starting dose is 0.5 mg PO twice a day during week one; increase to 1 mg PO twice a day or 2 mg PO once daily during week two. If a dose of at least 2 mg/day PO is well tolerated, 25 mg IM every 2 weeks of the depot injection may be started. Continue oral risperidone for 3 weeks after the first depot injection, then discontinue. A slower titration beginning with 12.5 mg IM may be more appropriate for some patients. Efficacy of the 12.5 mg dose has not been evaluated in clinical trials.

ADMINISTRATION

Oral Administration

Oral Solid Formulations

Conventional Tablets: May be administered without regard to meals.
Orally-disintegrating tablets (ODT, i.e., Risperdal M-tab):
Tablet strengths 0.5 mg, 1 mg, and 2 mg: Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. Do not push the tablet through the foil because this could damage the tablet. Using dry hands, remove the tablet from the blister unit and immediately place the entire tablet on the tongue. Allow the tablet to disintegrate in the mouth (will occur within seconds); the patient can then swallow the dissolved medicine with or without liquid. The patient should not split or chew the tablet.
Tablet strengths 3 mg and 4 mg: The child-resistant pouch should be torn open at the notch to access the blister. Do not open the blister until ready to administer. Peel back foil from the side to expose the tablet. Do not push the tablet through the foil because this could damage the tablet. Using dry hands, remove the tablet from the blister unit and immediately place the entire tablet on the tongue. Allow the tablet to disintegrate in the mouth (will occur within seconds); the patient can then swallow the dissolved medicine with or without liquid. The patient should not split or chew the tablet.

Oral Liquid Formulations

Oral solution (Risperdal oral solution):
Can be administered directly from the calibrated pipette, or can be mixed with a beverage prior to administration.
The minimum volume accurately measured with the pipette is 0.25 mL and the maximum is 3 mL.
Compatible beverages for dilution include water, coffee, orange juice, and low-fat milk. The solution is NOT compatible with cola or tea.

Injectable Administration

Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

Intramuscular Administration

Reconstitution, Preparation, and Administration Instructions for the Risperdal Consta dose pack:
Only for intramuscular administration; do not administer intravenously.
Risperdal Consta powder must only be suspended in the diluent provided by the manufacturer and administered with the supplied needle; do not substitute any components of the dose pack including the SmartSite Needle-Free Vial Access Device or Needle-Pro device. Use only the appropriate needle supplied in the dose pack for gluteal (2-inch needle) or deltoid (1-inch needle) administration.
All components of the dose pack are required for administration. Do not substitute any components.
To assure that the correct dose is delivered, the full contents of the vial must be administered.
It is recommended to administer the dose immediately after reconstitution.

Prior to admixing, remove the dose pack from the refrigerator and allow to come to room temperature for about 30 minutes prior to reconstitution.
Remove Flip off the plastic colored cap from the vial without removing the grey rubber stopper. Wipe top of the grey stopper with an alcohol wipe and allow to dry.
Peel back the blister pouch and remove the SmartSite Needle-Free Vial Access Device by holding between the white luer cap and the skirt. Do not touch the spike tip of the access device at any time.
It is very important for the SmartSite Needle-Free Vial Access Device to be placed on the vial correctly or the diluent could leak upon transfer to the vial.
Place the vial on a hard surface and hold the base. Orient the Vial Access Device vertically over the vial so that the spike tip is at the center of the vial's rubber stopper.
With a straight downward push, press the spike tip of the Vial Access Device through the center of the vial's rubber stopper until the device securely snaps onto the vial top. Improper placement of the Vial Access Device on the vial could result in leakage of the diluent upon transfer.
Hold the base of the vial and swab the syringe connection point (blue circle) of the Vial Access Device with an alcohol wipe and allow to dry prior to attaching the syringe to the Vial Access Device.
During syringe assembly steps, avoid over-tightening or syringe component parts may loosen from the syringe body.
For all syringe assembly steps, hold the syringe only by the white collar located at the tip of the syringe. Holding the white collar will help prevent the white collar from getting detached and ensure a good connection to the syringe.
To open the pre-filled syringe, hold the syringe only by the white collar and snap off the smooth white cap. Do not twist or cut off the white cap. Remove white cap together with the rubber tip cap inside.
While holding the white collar of the syringe, insert and press the syringe tip into the blue circle of the Vial Access Device and twist in a clockwise motion to secure the connection of the syringe to the Vial Access Device. Hold the skirt of the Vial Access Device during attachment to prevent it from spinning. Keep the syringe and the Vial Access Device aligned.
Inject the entire contents of the syringe containing the diluent into the vial.
Shake the vial vigorously for a minimum of 10 seconds while holding the plunger rod down with the thumb. Mixing is complete when the suspension appears uniform, thick, and milky colored, and all the powder is dispersed in liquid. The microspheres will be visible in liquid, but no dry microspheres remain.
Invert the vial completely and slowly withdraw the entire content of the suspension from the vial into the syringe. Tear the section of the vial label at the perforation and apply the detached label to the syringe for identification purposes.
While holding the white collar of the syringe, unscrew the syringe from the Vial Access Device, then discard both the vial and the Vial Access Device appropriately.
Select the appropriate color-coded needle provided with the kit. Two distinct needles are provided. The needle with the yellow colored hub and print is for injection into the gluteal muscle (2-inch needle) and the needle with the green colored hub and print is for deltoid muscles (1-inch needle). They are not interchangeable; do not use the needle intended for gluteal injection for deltoid injection, and vice versa.
Peel the blister pouch of the Needle-Pro safety device open halfway. Grasp the transparent needle sheath using the plastic peel pouch. To prevent contamination, do not touch the orange Needle-Pro safety device's luer connector. While holding the white collar of the syringe, attach the luer connection of the orange Needle-Pro safety device to the syringe with an easy clockwise twisting motion.
While holding the white collar of the syringe, grasp the transparent needle sheath and seat the needle firmly on the orange Needle-Pro safety device with a push and a clockwise twist. Seating the needle will secure the connection between the needle and the orange Needle-Pro safety device.
Re-suspension will be necessary prior to administration, since settling will occur after reconstitution. Re-suspend the microspheres in the syringe by shaking vigorously.
While holding the white collar of the syringe, pull the transparent needle sheath straight away from the needle. Do not twist the sheath since this may loosen the luer connection.
Remove any air bubbles by tapping the syringe and slowly depressing the plunger with the needle in an upright position.
Immediately inject the entire contents of the syringe into the upper outer quadrant of the gluteal area or the deltoid muscle of the arm; inject immediately after reconstitution to avoid settling. Gluteal injections should be alternated between the two buttocks.
To avoid a needle stick injury: do not use free hand to press the Needle-Pro safety device over the needle; do not intentionally disengage the Needle-Pro safety device; do not attempt to straighten the needle or engage the Needle-Pro safety device if the needle is bent or damaged; do not mishandle the Needle-Pro safety device since it may cause the needle to protrude from the Needle-Pro safety device.
Refer to the Instructions for Use section of the product labeling for detailed visual aides which accompany the written instructions.

Storage and Disposition Instructions for the Risperdal Consta dose pack:
After the injection is complete, press the needle into the orange Needle-Pro safety device by gently pressing the orange Needle-Pro safety device against a flat surface with one hand. As the orange Needle-Pro safety device is pressed, the needle will firmly engage into the orange Needle-Pro safety device.
Visually confirm full engagement of the needle into the orange Needle-Pro safety device, then appropriately discard both the used and unused needle provided in the dose pack.
Do not store the vial after reconstitution or the suspension may settle.
Do not combine 2 different dosage strengths of Risperdal Consta in a single administration.
The dose pack device is for single use only. Do not re-process for subsequent re-use because the integrity of the device may be compromised leading to a deterioration in performance.
Stability after reconstitution: Once in suspension, the product may remain at room temperature at or below 25 degrees C (77 degrees F), but must be used within 6 hours. Always re-suspend prior to administration if not used immediately.

STORAGE

Generic:
- Protect from light
- Protect from moisture
- Store at controlled room temperature (between 68 and 77 degrees F)

Risperdal:
- Protect from light
- Protect from moisture
- Store between 59 to 77 degrees F

Risperdal Consta:
- Discard product if it contains particulate matter, is cloudy, or discolored
- Discard reconstituted product if not used within 6 hours
- Protect from light
- Refrigerate (between 36 and 46 degrees F)
- Store at temperatures not exceeding 77 degrees F for no more than 7 days if refrigeration is not available

Risperdal M-Tab:
- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F

CONTRAINDICATIONS / PRECAUTIONS

General Information

Risperidone is contraindicated in patients with a known hypersensitivity to risperidone or paliperidone, or to any of the excipients in the risperidone formulation. Paliperidone is a metabolite of risperidone, and cross-sensitivity is possible. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone and paliperidone. In rare instances, anaphylactoid reactions have occurred after exposure to risperidone long-acting injection (Risperdal Consta) in patients who have previously tolerated oral risperidone.

CNS depression, coadministration with other CNS depressants, driving or operating machinery, ethanol ingestion

Risperidone has the potential to impair cognitive and motor skills. The sedative effects of risperidone may be most evident in the initial days of treatment. Patients should be advised to use caution when engaging in activities requiring coordination and concentration, such as driving or operating machinery, until they know how this drug affects them. Somnolence due to antipsychotic use could lead to falls with the potential for fractures and other injuries. A fall risk assessment should be completed when initiating an antipsychotic in patients with conditions, diseases, or concurrent medication use that could exacerbate somnolence. A fall risk assessment should be completed recurrently in at-risk patients on long-term antipsychotic therapy. In general, avoid use in patients with significant CNS depression. Given the primary CNS effects of risperidone, caution should be used during coadministration with other CNS depressants and alcohol. Ethanol ingestion may further impair cognitive and motor skills and patients should be advised to avoid use of alcoholic beverages.

Agranulocytosis, hematological disease, leukopenia, neutropenia, thrombotic thrombocytopenic purpura (TTP)

Risperidone should be used with caution in patients with hematological disease. Hematologic effects including leukopenia, neutropenia, and agranulocytosis have been associated with antipsychotic use. A history of drug-induced leukopenia or neutropenia or pre-existing low white blood cell (WBC) count may increase the likelihood of developing hematologic effects during treatment with an antipsychotic medication. Patients with a history of clinically significant low WBC count or drug-induced leukopenia/neutropenia should have frequent complete blood count (CBC) assessments during the first few months of treatment. Discontinuation of the antipsychotic should be considered if a clinically significant decline in WBC occurs in the absence of an identifiable cause. Patients with clinically significant neutropenia should be closely monitored for fever and infection, and appropriate medical intervention should be instituted if necessary. Risperidone should be discontinued in patients with severe neutropenia (ANC less than 1,000/mm3); ongoing medical care is recommended until the symptoms resolve. Although cases of thrombotic thrombocytopenic purpura (TTP) have been reported in association with risperidone administration, the relationship to drug therapy is unknown.

Phenylketonuria

Risperidone orally disintegrating tablets (e.g., Risperdal M-Tab ODT, others) contain aspartame, a source of phenylalanine. For example, Risperdal M-Tabs contain phenylalanine in the following quantities: each 4 mg ODT contains 0.84 mg phenylalanine; each 3 mg ODT contains 0.63 mg phenylalanine; each 2 mg ODT contains 0.42 mg phenylalanine; each 1 mg ODT contains 0.28 mg phenylalanine; and each 0.5 mg ODT contains 0.14 mg phenylalanine. Caution is advised in patients with phenylketonuria.

Suicidal ideation

Suicidal ideation is possible in patients with schizophrenia or bipolar disorder. Close supervision and control of medication is advisable. Prescribe risperidone in the smallest quantity consistent with good management in order to reduce the risk of overdose.

Abrupt discontinuation

Abrupt discontinuation of antipsychotics is generally not advisable unless required by the patient's medical condition. Abrupt discontinuation of antipsychotics can be associated with withdrawal dyskinesias and a risk of developing neuroleptic malignant syndrome. Because of the strong alpha-adrenergic receptor blocking effects of

risperidone, abrupt discontinuation may cause rebound anxiety, restlessness, sweating, tremors, abdominal pain, heart palpitations, headache, and increased blood pressure. During drug discontinuation, patients should be carefully observed for the recurrence of symptoms from the psychiatric disorder (e.g., schizophrenia, bipolar disorder) being treated. A drug withdrawal syndrome (unspecified) was reported during clinical trial evaluation of risperidone; however, the frequency is unknown and causality to the drug has not been established.

Tardive dyskinesia

Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotics. Periodic evaluation for movement disorders is recommended (e.g., AIMS). Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the initiation of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotics differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotics administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief periods at low doses or may even arise after drug discontinuation. The syndrome may remit, partially or completely, if the antipsychotic is withdrawn. Antipsychotics may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, risperidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotics, and for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic therapy, the smallest dose and the shortest duration producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear, risperidone discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

Cardiac disease, cerebrovascular disease, heart failure, hypovolemia, myocardial infarction, orthostatic hypotension, syncope

Secondary to alpha-blockade, risperidone can inhibit vasoconstriction and can produce vasodilation. The resultant drop in blood pressure through decreased peripheral resistance can precipitate orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope. This effect may especially occur during the initial dose-titration period. Limiting the initial risperidone dose and titration of the dosage according to recommended schedules might minimize the risk of orthostatic hypotension and syncope. Monitoring of orthostatic vital signs should be considered in patients for whom hypotension is of concern. Orthostatic hypotension could lead to falls with the potential for fractures and other injuries. A fall risk assessment should be completed when initiating an antipsychotic in patients with conditions, diseases, or concurrent medication use that could exacerbate orthostasis. A fall risk assessment should be completed recurrently in at-risk patients on long-term antipsychotic therapy. Patients should be counseled on measures to prevent orthostatic hypotension, such as sitting on the edge of the bed for several minutes prior to standing in the morning, or rising slowly from a seated position. Consider dose reduction if hypotension occurs. Use with particular caution in patients with known cardiac disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, or with conditions that would predispose patients to hypotension (e.g., dehydrated state or hypovolemia). Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications.

Alcoholism, bradycardia, cardiac arrhythmias, coronary artery disease, females, hypertension, hypocalcemia, hypokalemia, hypomagnesemia, long QT syndrome, malnutrition, QT prolongation, thyroid disease, torsade de pointes

Pooled data from controlled trials indicate there are no statistically significant differences in mean changes from baseline in ECG parameters including QT, QTc, and PR intervals when risperidone is compared to placebo. However, post-marketing reports of overdose indicate that QT prolongation and torsade de pointes have occurred. Causality to the drug has not been established. Use risperidone with caution in patients with cardiac disease or other conditions that may increase the risk of QT prolongation including cardiac arrhythmias, congenital long QT syndrome, heart failure, bradycardia, myocardial infarction, hypertension, coronary artery disease, hypomagnesemia, hypokalemia, hypocalcemia, or in patients receiving medications known to prolong the QT interval or cause electrolyte imbalances. Females, elderly patients, patients with diabetes, thyroid disease, malnutrition, alcoholism, or hepatic impairment may also be at increased risk for QT prolongation.

Hyponatremia, seizure disorder, seizures

In clinical trials, risperidone was associated with seizures in a small number of adult patients (0.3%); two cases occurred in association with hyponatremia. Seizures have also been reported during post-marketing use. For these reasons, patients with a seizure disorder, a condition that lowers seizure threshold, or uncorrected hyponatremia should be treated cautiously with risperidone.

Renal failure, renal impairment

Because risperidone and its active metabolite are substantially excreted by the kidneys, the risk of toxicity is greater in patients with renal impairment, including renal failure. In adult patients with moderate to severe renal impairment (CrCl 15 to 59 mL/minute), the clearance of risperidone and its active metabolite is decreased by 60% compared to healthy subjects. Reduced oral and injectable dosages are recommended for adult patients with severe renal impairment (CrCl less than 30 mL/minute). Guidelines for adjustments in pediatric patients are not available.

Hepatic disease

In adult patients with hepatic disease, the mean free fraction of risperidone in plasma is increased by about 35%. Therefore, reduced oral and injectable dosages are recommended for adult patients with hepatic disease. Guidelines for dosage adjustment in pediatric patients are not available.

Neurological disease, Parkinson's disease

Antipsychotics can cause motor and sensory instability, which may lead to falls with the potential for fractures and other injuries. A fall risk assessment should be completed when initiating an antipsychotic in patients with diseases (e.g., neurological disease), conditions, or concurrent medication use that could exacerbate motor and sensory instability. A fall risk assessment should be completed recurrently in at-risk patients on long-term antipsychotic therapy. Risperidone should be used with caution in patients with Parkinson's disease because of possible development of extrapyramidal symptoms. However, atypical antipsychotics like risperidone are less likely to interfere with treatments for Parkinson's disease than traditional antipsychotic agents. Patients with Parkinson's disease are thought to experience an increased sensitivity to antipsychotics manifest as confusion, obtundation, postural instability with frequent falls, extrapyramidal effects, and symptoms resembling neuroleptic malignant syndrome. In general, avoid risperidone use during therapy for Parkinson's disease unless the benefit of the drug outweighs the risk of decreased therapeutic response to levodopa or other treatments.

Dementia, geriatric, stroke

Lower initial doses of risperidone are recommended in geriatric patients due to decreased medication clearance in this population and a greater frequency of hepatic, renal and cardiac dysfunction, concomitant chronic disease, and other drug therapy. To decrease the incidence of orthostatic hypotension, careful titration of risperidone dosage is recommended. Antipsychotics, like risperidone, are not approved for the treatment of dementia-related psychosis in geriatric patients. In April 2005 the FDA mandated that all manufacturers of atypical antipsychotics include a boxed warning to the labeling indicating that increased death rates (1.6 to 1.7 times that of placebo) have been noted in this patient population receiving atypical antipsychotics. Death typically occurred due to heart failure, sudden death, or infections (primarily pneumonia). Of 17 placebo controlled trials (n = 5,106) performed with olanzapine, aripiprazole, risperidone, or quetiapine in elderly patients with dementia-related psychosis, 15 showed numerical increases in mortality in the active compared to the placebo-treated patients. In June 2008, FDA required manufacturers of conventional antipsychotics to also add a boxed warning to their product labeling regarding an increased risk of death in elderly patients with dementia. A significantly increased incidence of cerebrovascular events (stroke, transient ischemia attack) have been reported in the elderly with dementia-related psychosis taking risperidone vs. placebo (n = 1,230). Some events have been fatal; use risperidone with extreme caution in elderly patients with cerebrovascular disease. Patients with Dementia with Lewy Bodies are thought to experience an increased sensitivity to antipsychotics manifest as confusion, obtundation, postural instability with frequent falls, extrapyramidal effects, and symptoms resembling neuroleptic malignant syndrome. According to the Beers Criteria, antipsychotics are considered potentially inappropriate medications (PIMs) in elderly patients, and use should be avoided except for treating schizophrenia or bipolar disorder, and for short-term use as antiemetics during chemotherapy. In addition, avoidance of risperidone is recommended in geriatric patients with the following disease states or symptoms due to the potential for exacerbation of the condition or increased risk of adverse effects: Parkinson's disease (symptom exacerbation), delirium (possible new-onset or worsening delirium), and dementia (adverse CNS effects). There is an increased risk of stroke and greater rate of cognitive decline and mortality in persons with dementia receiving antipsychotics, and the Beers expert panel recommends avoiding antipsychotics to treat delirium- or dementia-related behavioral problems unless non-pharmacological options have failed or are not possible and the patient is a substantial threat to self or others. The Panel recommends avoiding antipsychotics in elderly patients with a history of falls or fractures, unless safer alternatives are not available, since antipsychotics can cause ataxia, impaired psychomotor function, syncope, and additional falls; if an antipsychotic must be used, consider reducing use of other CNS-active medications that increase the risk of falls and fractures and implement other strategies to reduce fall risk. Because antipsychotics can cause or exacerbate hyponatremia and SIADH and the elderly are at increased risk of developing these conditions, sodium levels should be closely monitored when starting or changing dosages of antipsychotics in older adults. The federal Omnibus Budget Reconciliation Act (OBRA) regulates medication use in residents of long-term care facilities (LTCFs). An antipsychotic should generally be used only for the conditions listed in the guidelines (e.g., schizophrenia, mood disorder, Tourette's disorder) and that meet the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for use. There is an increased risk of morbidity and mortality in elderly patients treated with antipsychotics for dementia-related psychosis. Therefore, identify and address all possible causes of behavioral or psychological symptoms of dementia (BPSD) before considering an antipsychotic. To initiate antipsychotic therapy, behavioral symptoms must be a danger to self or others and are either 1) due to mania or psychosis or 2) the plan of care includes documentation of attempted behavioral interventions (except in an emergency). Limit emergency treatment to 7 days or less with evaluation and documentation within 7 days which identifies and addresses contributors/causes. For acute conditions persisting beyond 7 days, pertinent non-pharmacologic interventions must be attempted, unless clinically contraindicated, and documented. Treatment of non-acute, chronic, or prolonged BPSD must meet all of the OBRA criteria for BPSD treatment, and include monitoring that ensures the behavioral symptoms are not due to a treatable or correctable medical condition, are not due to correctable environmental or treatable psychological stressors alone, and provides clearly documented evidence of persistence. The LTCF must evaluate the appropriateness of the antipsychotic during or within 2 weeks of admission for a newly admitted resident on an antipsychotic. In all cases, the lowest possible dose and shortest duration should be prescribed. OBRA provides general dosing guidance for antipsychotic treatment of BPSD. Monitoring of antipsychotics should include evaluation of ongoing effectiveness, rationale for use, and potential adverse effects (e.g., anticholinergic effects, neurological symptoms, metabolic syndrome, cardiac effects). Antipsychotics are subject to periodic review for effectiveness, necessity, and the potential for gradual dose reduction (GDR) or discontinuation. Refer to the OBRA guidelines for complete information.

Dysphagia

Patients with dysphagia or who are at risk for aspiration pneumonia should be closely monitored while receiving risperidone. Antipsychotic drug use has been associated with esophageal dysmotility and aspiration of gastric contents, which may increase the incidence of aspiration pneumonia in certain patient populations, such as patients with advanced Alzheimer's disease.

Ambient temperature increase, dehydration, hyperthermia, hypothermia, strenuous exercise

Antipsychotics have been reported to disrupt the body's ability to reduce core body temperature presumably through effects in the hypothalamus, and they predispose patients to hyperthermia. Patients receiving risperidone should be advised of conditions that contribute to an elevation in core body temperature (e.g., strenuous exercise, ambient temperature increase, or dehydration). A less frequently described alteration in thermoregulatory processes reported with both conventional and atypical antipsychotics is hypothermia. Thermoregulation is multi-factorial; however, the dopaminergic system appears to have a primary role, and serotonin may also have modulatory activity (5-HT2a receptors). Most cases of hypothermia associated with antipsychotics have occurred in conjunction with other potential precipitating factors such as hypothyroidism, sepsis, organic brain injury, or environmental temperature. Hypothermia appears to occur more frequently during initiation of antipsychotic therapy or after dose increases.

Diabetes mellitus, diabetic ketoacidosis, hypercholesterolemia, hyperglycemia, hyperlipidemia, hyperosmolar hyperglycemic state (HHS), hypertriglyceridemia, obesity

Atypical antipsychotics, including risperidone, have been associated with metabolic changes that may increase cardiovascular or cerebrovascular risk over time, including loss of blood glucose control, dyslipidemia and weight gain. Hyperglycemia and diabetes mellitus, in some cases associated with diabetic ketoacidosis, hyperosmolar hyperglycemic state (HHS) with coma or death, have been reported in patients treated with atypical antipsychotics including risperidone. Epidemiological studies suggest an increased risk of hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. An increased risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in general complicates this concern. All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness). Patients with established diabetes mellitus who are started on atypical antipsychotics, such as risperidone, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, pre-diabetes, family history) should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the antipsychotic was discontinued; however, some patients required continuation of anti-diabetics despite discontinuation of the suspect drug. Treatment with risperidone should be undertaken with caution in patients with pre-existing conditions such as obesity, pre-diabetes, or hyperlipidemia (e.g., hypercholesterolemia or hypertriglyceridemia).

Breast cancer, hyperprolactinemia, infertility

Risperidone can cause hyperprolactinemia, likely due to central dopamine D2 receptor antagonism, and is associated with higher elevations in prolactin than many other antipsychotics. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Elevations in prolactin may result in infertility in either men or women, or other endocrine abnormalities in adults and pediatric patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. Close monitoring for adverse endocrine effects is advisable during use of risperidone. In animal studies, an increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia was observed during risperidone administration. Some human breast cancers may be prolactin-dependent and therefore risperidone should be used cautiously in those who have a history of breast cancer.

Intravenous administration, subcutaneous administration

Parenteral risperidone (Risperdal Consta) is for intramuscular administration only. Do not give via intravenous administration or subcutaneous administration.

Priapism

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported during post-marketing use of risperidone. Priapism requires medical treatment and severe cases may require surgical intervention. Advise male patients to seek medical intervention if they experience a prolonged or painful erection lasting more than 4 hours. The patient should call their healthcare provider or go to the nearest emergency room right away if this occurs.

Neonates, pregnancy, pregnancy testing

Data are insufficient to establish the safe use of risperidone during human pregnancy. Because risperidone is known to cross the placenta in animals, use during pregnancy should only occur when the benefits outweigh the risks. No teratogenic effects were observed in animal studies; however, an increase in stillborn rat pups occurred at all doses studied. Increases in the incidence of pituitary gland, pancreas, and mammary gland neoplasms have been found in rodents after chronic administration of risperidone and some other antipsychotics and may be mediated by prolactin. The relevance of these findings in humans is unknown. There is a human case report of agenesis of the corpus callosum occurring in utero. Neonates exposed to antipsychotics during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery.

There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity and have ranged from self-limited to those requiring intensive care unit support and prolonged hospitalization. Neonates exhibiting signs or symptoms of extrapyramidal effects or withdrawal should be carefully monitored. The knowledge about long-term neurobehavioral effects in offspring is limited for all antipsychotic agents and requires further investigation. According to the American Psychiatric Association treatment guidelines for schizophrenia, consider pregnancy testing in women of childbearing potential prior to initiation of an antipsychotic. The National Pregnancy Registry for Psychiatric Medications is dedicated to evaluating the safety of psychiatric medications that may be taken by women during pregnancy to treat a wide range of mood, anxiety, or psychiatric disorders. The primary goal of this Registry is to determine the frequency of major malformations, such as heart defects, cleft lip, or neural tube defects, in babies exposed to various psychiatric drugs during pregnancy. While the research concentrates on atypical antipsychotics and antidepressant use, pregnant women using other psychiatric medications are encouraged to register. For more information, contact the registry at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry or by phone 1-866-961-2388. It is not known if antipsychotics, through their effect on prolactin, would affect labor or delivery.

Breast-feeding

According to the manufacturer of oral risperidone, a decision should be made whether to discontinue breast-feeding or to discontinue the drug taking into account the importance of the drug to the mother. Risperidone and 9-hydroxyrisperidone are present in human breast milk and there is a potential for serious adverse reactions in the nursing infant. The manufacturer of the depot risperidone injection (Risperdal Consta) states that breast-feeding should not occur for at least 12 weeks after the last injection. Antipsychotics may cause elevated prolactin levels and galactorrhea to varying degrees, and thus may interfere with proper lactation. Four case reports document the excretion of risperidone and 9-hydroxyrisperidone into breast milk; the milk/plasma ratio for all 4 women was less than 0.5 for both compounds. The calculated relative doses each infant received were 2.3, 2.8, 4.3 and 4.7% of the maternal doses (weight adjusted). When the infant plasma samples were assayed, risperidone and 9-hydroxyrisperidone were not detectable. Each infant was thriving and no reported adverse effects were attributable to risperidone. According to the authors, maternal use of risperidone is unlikely to be a significant risk for the breast-fed infant in the short-term, but long-term risks are unknown and the potential risks/benefits should be evaluated. Due to individual variability in response to antipsychotics, it may be prudent to continue the existing regimen if ongoing treatment is deemed necessary during breast-feeding. However, if an alternative antipsychotic is needed, other atypical agents such as olanzapine or quetiapine may be considered. Data related to the safety of antipsychotics during breast-feeding are limited and chronic administration of any antipsychotic during breast-feeding should be avoided if possible. Regardless of the antipsychotic used, the nursing infant should be closely monitored for excessive drowsiness, lethargy, and developmental delays. Combination treatment with antipsychotics may increase the risk of these adverse events. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Children

Oral administration of risperidone is FDA approved for use in children 10 years of age and older with bipolar disorder, adolescents 13 years of age and older with schizophrenia, and for irritability associated with autistic disorder in pediatric patients 5 years of age and older. Safety and effectiveness of Risperdal Consta injection in pediatric patients have not been established. Risperidone has been associated with hyperprolactinemia in children and adolescents. Sequelae have included galactorrhea and gynecomastia. During clinical trials in children 5 to 17 years of age, 49% of risperidone-treated patients had elevated prolactin levels versus 2% who received placebo. Other study data in children and adolescents with bipolar disorder or schizophrenia indicate that 82% to 87% of patients receiving risperidone experienced elevated prolactin levels (vs. 3 to 7% of those who received placebo). During clinical trials that included 1,885 children and adolescents, galactorrhea and gynecomastia were reported in 0.8% and 2.3% of risperidone-treated patients, respectively. Weight gain in children and adolescents may be substantial, particularly during chronic treatment. The long-term effects of risperidone on growth and sexual maturation have not been fully evaluated; however, decreases in bone length and density, delays in sexual maturation, and impairment in cognitive performance have been documented in studies in juvenile animals. Close monitoring for adverse endocrine effects is advisable during use of risperidone in children and adolescents. Weight gain should be evaluated against expected normal growth patterns in pediatric patients.

ADVERSE REACTIONS

Severe

tardive dyskinesia / Delayed / 0.8-5.3
seizures / Delayed / 0.3-0.3
tissue necrosis / Early / Incidence not known
akinesia / Delayed / Incidence not known
neuroleptic malignant syndrome / Delayed / Incidence not known
SIADH / Delayed / Incidence not known
water intoxication / Delayed / Incidence not known
bradycardia / Rapid / Incidence not known
cardiac arrest / Early / Incidence not known
AV block / Early / Incidence not known
atrial fibrillation / Early / Incidence not known
torsade de pointes / Rapid / Incidence not known
anaphylactoid reactions / Rapid / Incidence not known
thrombotic thrombocytopenic purpura (TTP) / Delayed / Incidence not known

angioedema / Rapid / Incidence not known
ileus / Delayed / Incidence not known
GI obstruction / Delayed / Incidence not known
rhabdomyolysis / Delayed / Incidence not known
agranulocytosis / Delayed / Incidence not known
ocular hypertension / Delayed / Incidence not known
retinal thrombosis / Delayed / Incidence not known
visual impairment / Early / Incidence not known
diabetic ketoacidosis / Delayed / Incidence not known
pancreatitis / Delayed / Incidence not known
stroke / Early / Incidence not known
pulmonary embolism / Delayed / Incidence not known
apnea / Delayed / Incidence not known

Moderate

pseudoparkinsonism / Delayed / 6.0-28.0
constipation / Delayed / 5.0-17.0
akathisia / Delayed / 0-11.0
urinary incontinence / Early / 1.0-7.0
blurred vision / Early / 1.0-7.0
hyperlipidemia / Delayed / 2.5-6.3
hypercholesterolemia / Delayed / 4.3-6.3
dystonic reaction / Delayed / 2.0-6.0
sinus tachycardia / Rapid / 1.0-3.0
hypertension / Early / 3.0-3.0
cystitis / Delayed / 1.0-3.0
hypertriglyceridemia / Delayed / 2.5-2.7
chest pain (unspecified) / Early / 2.0-2.0
orthostatic hypotension / Delayed / 0-2.0
dyspnea / Early / 1.0-2.0
anemia / Delayed / 0-1.0
hyperglycemia / Delayed / 0-0.8
diabetes mellitus / Delayed / 0-0.4
hyperprolactinemia / Delayed / 10.0
skin ulcer / Delayed / Incidence not known
hematoma / Early / Incidence not known
depression / Delayed / Incidence not known
confusion / Early / Incidence not known
mania / Early / Incidence not known
dysarthria / Delayed / Incidence not known
dysphonia / Delayed / Incidence not known
dyskinesia / Delayed / Incidence not known
hyperthermia / Delayed / Incidence not known
edema / Delayed / Incidence not known
peripheral edema / Delayed / Incidence not known
hypotension / Rapid / Incidence not known
bundle-branch block / Early / Incidence not known
QT prolongation / Rapid / Incidence not known
galactorrhea / Delayed / Incidence not known
precocious puberty / Delayed / Incidence not known
infertility / Delayed / Incidence not known
urinary retention / Early / Incidence not known
impotence (erectile dysfunction) / Delayed / Incidence not known
priapism / Early / Incidence not known
dysuria / Early / Incidence not known
ejaculation dysfunction / Delayed / Incidence not known
eosinophilia / Delayed / Incidence not known
erythema / Early / Incidence not known
atopic dermatitis / Delayed / Incidence not known
dysphagia / Delayed / Incidence not known
pneumonitis / Delayed / Incidence not known
fecal incontinence / Early / Incidence not known
gastritis / Delayed / Incidence not known
myasthenia / Delayed / Incidence not known
neutropenia / Delayed / Incidence not known
leukopenia / Delayed / Incidence not known
thrombocytopenia / Delayed / Incidence not known
conjunctival hyperemia / Early / Incidence not known
conjunctivitis / Delayed / Incidence not known
photophobia / Early / Incidence not known
glycosuria / Early / Incidence not known
hypoglycemia / Early / Incidence not known
elevated hepatic enzymes / Delayed / Incidence not known
jaundice / Delayed / Incidence not known
wheezing / Rapid / Incidence not known

ocular infection / Delayed / Incidence not known
withdrawal / Early / Incidence not known

Mild

drowsiness / Early / 5.0-63.0
appetite stimulation / Delayed / 4.0-44.0
insomnia / Early / 24.0-32.0
fatigue / Early / 1.0-31.0
headache / Early / 12.0-21.0
vomiting / Early / 10.0-20.0
cough / Delayed / 2.0-17.0
anxiety / Delayed / 0-16.0
dizziness / Early / 3.0-16.0
nausea / Early / 3.0-16.0
abdominal pain / Early / 13.0-16.0
fever / Early / 1.0-16.0
rhinorrhea / Early / 12.0-12.0
tremor / Early / 0-11.0
dyspepsia / Early / 3.0-10.0
xerostomia / Early / 0-10.0
hypersalivation / Early / 0-10.0
nasal congestion / Early / 4.0-10.0
rhinitis / Early / 9.0-9.0
weight gain / Delayed / 4.0-8.0
rash (unspecified) / Early / 0-8.0
diarrhea / Early / 1.0-8.0
polydipsia / Early / 0-7.0
nocturia / Early / 7.0-7.0
anorexia / Delayed / 6.0-6.0
injection site reaction / Rapid / 1.0-4.0
weight loss / Delayed / 1.0-4.0
amenorrhea / Delayed / 4.0-4.0
back pain / Delayed / 1.0-4.0
xerosis / Delayed / 0-3.0
dental pain / Delayed / 1.0-3.0
arthralgia / Delayed / 2.0-3.0
asthenia / Delayed / 1.0-2.0
hypoesthesia / Delayed / 0-2.0
lethargy / Early / 2.0-2.0
syncope / Early / 1.0-2.0
acne vulgaris / Delayed / 2.0-2.0
epistaxis / Delayed / 0-2.0
sinusitis / Delayed / 1.0-2.0
agitation / Early / Incidence not known
vertigo / Early / Incidence not known
paresthesias / Delayed / Incidence not known
hypothermia / Delayed / Incidence not known
malaise / Early / Incidence not known
chills / Rapid / Incidence not known
tinnitus / Delayed / Incidence not known
otalgia / Early / Incidence not known
gynecomastia / Delayed / Incidence not known
oligomenorrhea / Delayed / Incidence not known
menorrhagia / Delayed / Incidence not known
breast enlargement / Delayed / Incidence not known
vaginal discharge / Delayed / Incidence not known
libido decrease / Delayed / Incidence not known
menstrual irregularity / Delayed / Incidence not known
orgasm dysfunction / Delayed / Incidence not known
increased urinary frequency / Early / Incidence not known
pruritus / Rapid / Incidence not known
maculopapular rash / Early / Incidence not known
skin hyperpigmentation / Delayed / Incidence not known
skin discoloration / Delayed / Incidence not known
hyperkeratosis / Delayed / Incidence not known
photosensitivity / Delayed / Incidence not known
seborrhea / Delayed / Incidence not known
alopecia / Delayed / Incidence not known
cheilitis / Delayed / Incidence not known
dysgeusia / Early / Incidence not known
myalgia / Early / Incidence not known
lacrimation / Early / Incidence not known
blepharedema / Early / Incidence not known
ocular discharge / Delayed / Incidence not known
xerophthalmia / Early / Incidence not known

polyuria / Early / Incidence not known
flushing / Rapid / Incidence not known
hyperventilation / Early / Incidence not known
pharyngitis / Delayed / Incidence not known
infection / Delayed / Incidence not known
influenza / Delayed / Incidence not known

DRUG INTERACTIONS

Abarelix: (Major) Since abarelix can cause QT prolongation, abarelix should be used cautiously, if at all, with other drugs that are associated with QT prolongation including risperidone. Prescribers need to weigh the potential benefits and risks of abarelix use in patients that are taking drugs that can cause QT prolongation.
Acarbose: (Moderate) Patients taking alpha-glucosidase inhibitors should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.
Acebutolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of acebutolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving acebutolol concomitantly.
Acetaminophen; Butalbital: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.
Acetaminophen; Butalbital; Caffeine: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.
Acetaminophen; Butalbital; Caffeine; Codeine: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials. (Moderate) Concomitant use of codeine with other central nervous system (CNS) depressants, such as risperidone, can potentiate the effects of codeine and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of codeine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of codeine and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
Acetaminophen; Caffeine; Dihydrocodeine: (Moderate) Additive CNS depression may occur if opiate agonists are used concomitantly with risperidone. The dose of one or both drugs should be reduced.
Acetaminophen; Caffeine; Magnesium Salicylate; Phenyltoloxamine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Acetaminophen; Caffeine; Phenyltoloxamine; Salicylamide: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine: (Moderate) Due to the primary

CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known. (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.

Acetaminophen; Codeine: (Moderate) Concomitant use of codeine with other central nervous system (CNS) depressants, such as risperidone, can potentiate the effects of codeine and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of codeine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of codeine and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

Acetaminophen; Dextromethorphan; Doxylamine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.

Acetaminophen; Dichloralphenazone; Isometheptene: (Moderate) Drugs that can cause CNS depression, including dichloralphenazone, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness if used concomitantly with atypical antipsychotics.

Acetaminophen; Diphenhydramine: (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as diphenhydramine. This combination is commonly used in clinical practice; however, additive drowsiness or other CNS effects may occur. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.

Acetaminophen; Hydrocodone: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone.

Acetaminophen; Oxycodone: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as risperidone, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of oxycodone in patients taking risperidone, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Oxycodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate oxycodone at one-third to one-half the usual dosage in patients that are concurrently receiving another CNS depressant. Also, consider using a lower risperidone dose. Monitor patients for sedation and respiratory depression.

Acetaminophen; Pentazocine: (Moderate) Coadministration of pentazocine with atypical antipsychotics may result in additive respiratory and CNS depression and anticholinergic effects, such as urinary retention and constipation. Use pentazocine with caution in any patient receiving medication with CNS depressant and/or anticholinergic activity.

Acetaminophen; Propoxyphene: (Moderate) Concomitant use of propoxyphene with other CNS depressants, such as risperidone, can potentiate the effects of propoxyphene on respiratory depression and/or sedation.

Acetaminophen; Tramadol: (Major) Concurrent use of tramadol and risperidone should be avoided if possible due to a possible increased risk of seizures. Seizures have been reported in patients receiving monotherapy with tramadol or antipsychotics at recommended doses. In addition, due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally-acting medications such as tramadol.

Acrivastine; Pseudoephedrine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.

Albiglutide: (Moderate) Patients taking incretin mimetics should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Changes in lipid profiles and weight may also aggravate diabetes or associated conditions or complications. Temporal associations of atypical antipsychotic therapy with the aggravation or new onset of diabetes mellitus have been reported.

Albuterol: (Minor) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Albuterol; Ipratropium: (Minor) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and

the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Aldesleukin, IL-2: (Moderate) Aldesleukin, IL-2 may affect CNS function significantly. Therefore, psychotropic pharmacodynamic interactions could occur following concomitant administration of drugs with significant CNS or psyhcotropic activity. Use with caution.

Alfentanil: (Moderate) Due to the sedative effects of risperidone, caution should be used when risperidone is given in combination with other centrally-acting medications including opiate agonists such as alfentanil.

Alfuzosin: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include alfuzosin. Based on electrophysiology studies performed by the manufacturer, alfuzosin has a slight effect to prolong the QT interval. The QT prolongation appeared less with alfuzosin 10 mg than with 40 mg.

Aliskiren; Amlodipine: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Aliskiren; Amlodipine; Hydrochlorothiazide, HCTZ: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Alogliptin: (Moderate) Patients taking alogliptin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition.

Alogliptin; Metformin: (Moderate) Patients taking alogliptin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. (Moderate) Patients taking metformin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Alogliptin; Pioglitazone: (Moderate) Because risperidone has been associated with hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic states, diabetic coma, and overall worsening of glycemic control, patients taking antidiabetic agents such as thiazolidinediones should be closely monitored for worsening glycemic control when risperidone is instituted. Possible mechanisms for risperidone-related effects on glycemic control include insulin resistance or direct beta-cell inhibition. (Moderate) Patients taking alogliptin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition.

Alpha-glucosidase Inhibitors: (Moderate) Patients taking alpha-glucosidase inhibitors should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Alprazolam: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.

Amiodarone: (Major) Avoid coadministration of amiodarone and risperidone if possible due to the potential for an increased risk of QT prolongation and torsade de pointes (TdP). If coadministration is necessary, and the patient has known risk factors for cardiac disease or arrhythmia, then closely monitor for QT interval prolongation and adjust the risperidone dosage as appropriate. Risperidone has been associated with a possible risk for QT prolongation and TdP; however, data are primarily in the overdose setting. Amiodarone is associated with a well-established risk of QT prolongation and TdP. Due to the extremely long half-life of amiodarone, a drug interaction is possible for days to weeks after discontinuation of amiodarone.

Amitriptyline: (Moderate) Concurrent use of risperidone and tricyclic antidepressants should be approached with caution. Risperidone has a possible risk for QT prolongation and torsade de pointes and tricyclic antidepressants have rarely been associated with these effects, particularly when given in excessive doses or following overdose. No dosage adjustment of risperidone is recommended based on pharmacokinetic data; however, additive CNS effects are possible.

Amitriptyline; Chlordiazepoxide: (Moderate) Concurrent use of risperidone and tricyclic antidepressants

should be approached with caution. Risperidone has a possible risk for QT prolongation and torsade de pointes and tricyclic antidepressants have rarely been associated with these effects, particularly when given in excessive doses or following overdose. No dosage adjustment of risperidone is recommended based on pharmacokinetic data; however, additive CNS effects are possible. (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.

Amlodipine: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Amlodipine; Atorvastatin: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Amlodipine; Benazepril: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Amlodipine; Hydrochlorothiazide, HCTZ; Olmesartan: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Amlodipine; Hydrochlorothiazide, HCTZ; Valsartan: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Amlodipine; Olmesartan: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Amlodipine; Telmisartan: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Amlodipine; Valsartan: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Amobarbital: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.

Amoxapine: (Moderate) Use caution during co-administration of amoxapine and risperidone. Amoxapine exhibits some antipsychotic activity and may increase the risk of tardive dyskinesia or neuroleptic malignant syndrome (NMS) when antipsychotics are given concurrently. CNS effects, orthostatic hypotension, anticholinergic effects, and lowering of seizure threshold are potential problems with the combined use of amoxapine and antipsychotics.

Amoxicillin; Clarithromycin; Lansoprazole: (Major) Due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering clarithromycin with risperidone. If coadministration is considered necessary, and the patient has known risk factors for cardiac disease or arrhythmia, then close monitoring is essential. Clarithromycin is associated with an established risk for QT prolongation and TdP. Risperidone has been associated with a possible risk for QT prolongation and/or TdP; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting.

Amoxicillin; Clarithromycin; Omeprazole: (Major) Due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering clarithromycin with risperidone. If coadministration is considered necessary, and the patient has known risk factors for cardiac disease or arrhythmia, then close monitoring is essential. Clarithromycin is associated with an established risk for QT prolongation and TdP. Risperidone has been associated with a possible risk for QT prolongation and/or TdP; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting.

Amphetamine: (Major) Concurrent use of antipsychotics and amphetamines should generally be avoided. Antipsychotics and amphetamines may interact pharmacodynamically to diminish the therapeutic effects of either agent through opposing effects on dopamine. Amphetamines are thought to block central dopamine reuptake, which has the potential to exacerbate psychosis, and antipsychotics, which are central dopamine antagonists, may diminish the effectiveness of amphetamines.

Amphetamine; Dextroamphetamine: (Major) Concurrent use of antipsychotics and amphetamines should generally be avoided. Antipsychotics and amphetamines may interact pharmacodynamically to diminish the therapeutic effects of either agent through opposing effects on dopamine. Amphetamines are thought to block

central dopamine reuptake, which has the potential to exacerbate psychosis, and antipsychotics, which are central dopamine antagonists, may diminish the effectiveness of amphetamines.
Amphetamines: (Major) Concurrent use of antipsychotics and amphetamines should generally be avoided. Antipsychotics and amphetamines may interact pharmacodynamically to diminish the therapeutic effects of either agent through opposing effects on dopamine. Amphetamines are thought to block central dopamine reuptake, which has the potential to exacerbate psychosis, and antipsychotics, which are central dopamine antagonists, may diminish the effectiveness of amphetamines.
Anagrelide: (Major) Torsades de pointes (TdP) and ventricular tachycardia have been reported during post-marketing use of anagrelide. A cardiovascular examination, including an ECG, should be obtained in all patients prior to initiating anagrelide therapy. Monitor patients during anagrelide therapy for cardiovascular effects and evaluate as necessary. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with anagrelide include risperidone.
Angiotensin II receptor antagonists: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of angiotensin II receptor antagonists. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving angiotensin II receptor antagonists concomitantly.
Angiotensin-converting enzyme inhibitors: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Apomorphine: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include apomorphine. Apomorphine causes considerable somnolence, and concomitant administration of apomorphine and CNS depressants like the antipsychotics could result in additive CNS effects. Limited data indicate that QT prolongation is possible with apomorphine administration; the change in QTc interval is not significant in most patients receiving dosages within the manufacturer's guidelines; however, large increases (> 60 msecs from pre-dose) have occurred. Doses <= 6 mg SC are associated with minimal increases in QTc; doses > 6 mg SC do not provide additional clinical benefit and are not recommended.
Aprepitant, Fosaprepitant: (Major) Use caution if risperidone and aprepitant, fosaprepitant are used concurrently and monitor for an increase in risperidone-related adverse effects, including QT prolongation and torsade de pointes (TdP), for several days after administration of a multi-day aprepitant regimen. Risperidone is a CYP3A4 substrate. Aprepitant, when administered as a 3-day oral regimen (125 mg/80 mg/80 mg), is a moderate CYP3A4 inhibitor and inducer and may increase plasma concentrations of risperidone. For example, a 5-day oral aprepitant regimen increased the AUC of another CYP3A4 substrate, midazolam (single dose), by 2.3-fold on day 1 and by 3.3-fold on day 5. After a 3-day oral aprepitant regimen, the AUC of midazolam (given on days 1, 4, 8, and 15) increased by 25% on day 4, and then decreased by 19% and 4% on days 8 and 15, respectively. As a single 125 mg or 40 mg oral dose, the inhibitory effect of aprepitant on CYP3A4 is weak, with the AUC of midazolam increased by 1.5-fold and 1.2-fold. After administration, fosaprepitant is rapidly converted to aprepitant and shares many of the same drug interactions. However, as a single 150 mg intravenous dose, fosaprepitant only weakly inhibits CYP3A4 for a duration of 2 days; there is no evidence of CYP3A4 induction. Fosaprepitant 150 mg IV as a single dose increased the AUC of midazolam (given on days 1 and 4) by approximately 1.8-fold on day 1; there was no effect on day 4. Less than a 2-fold increase in the midazolam AUC is not considered clinically important.
Arformoterol: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.
Aripiprazole: (Major) QT prolongation has occurred during therapeutic use of aripiprazole and following overdose. Risperidone is an atypical antipsychotics with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with aripiprazole. In addition, caution is advisable when aripiprazole is given in combination with other CNS depressants such as other atypical antipsychotics. The risk of drowsiness, dizziness, hypotension, extrapyramidal symptoms, anticholinergic effects, neuroleptic malignant syndrome, tardive dyskinesia, or seizures may be increased during combined use; therefore, it may be advisable to initiate treatment with lower dosages if combination therapy is deemed necessary. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent.
Arsenic Trioxide: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If possible, drugs that are known to prolong the QT interval should be discontinued prior to initiating arsenic trioxide therapy. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include arsenic trioxide.

Artemether; Lumefantrine: (Major) Concomitant use of drugs with a possible risk of QT prolongation and torsade de pointes, including artemether; lumefantrine and risperidone, should be avoided if possible. Consider ECG monitoring if risperidone must be used with artemether; lumefantrine.
Articaine; Epinephrine: (Major) The alpha-adrenergic effects of epinephrine can be blocked during concurrent administration of risperidone. This blockade can cause an apparently paradoxical condition called 'epinephrine reversal'. The vasoconstrictive properties of dopamine infusion can be decreased due to the alpha-adrenergic blocking capability of risperidone. The use of other agents for vascular support is recommended when needed.
Asenapine: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer primarily in the overdosage setting. Asenapine has been associated with QT prolongation. According to the manufacturer, asenapine should not be used with other agents also known to have this effect. Co-administration of asenapine with risperidone may also increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.
Aspirin, ASA; Butalbital; Caffeine: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.
Aspirin, ASA; Butalbital; Caffeine; Codeine: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials. (Moderate) Concomitant use of codeine with other central nervous system (CNS) depressants, such as risperidone, can potentiate the effects of codeine and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of codeine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of codeine and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
Aspirin, ASA; Caffeine; Dihydrocodeine: (Moderate) Additive CNS depression may occur if opiate agonists are used concomitantly with risperidone. The dose of one or both drugs should be reduced.
Aspirin, ASA; Carisoprodol; Codeine: (Moderate) Concomitant use of codeine with other central nervous system (CNS) depressants, such as risperidone, can potentiate the effects of codeine and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of codeine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of codeine and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
Aspirin, ASA; Oxycodone: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as risperidone, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of oxycodone in patients taking risperidone, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Oxycodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate oxycodone at one-third to one-half the usual dosage in patients that are concurrently receiving another CNS depressant. Also, consider using a lower risperidone dose. Monitor patients for sedation and respiratory depression.
Atazanavir: (Major) Avoid coadministration of atazanavir and risperidone when possible. Caution should be used in patients receiving atazanavir concurrently with drugs metabolized via CYP3A4 and known to cause QT prolongation. Atazanavir inhibits the CYP3A4 isoenzyme at clinically relevant concentrations, which may lead to increased serum concentrations of risperidone and an increased potential for QT prolongation or other adverse effects. Serious and/or life-threatening drug interactions could potentially occur between atazanavir and risperidone.
Atazanavir; Cobicistat: (Major) Avoid coadministration of atazanavir and risperidone when possible. Caution should be used in patients receiving atazanavir concurrently with drugs metabolized via CYP3A4 and known to cause QT prolongation. Atazanavir inhibits the CYP3A4 isoenzyme at clinically relevant concentrations, which may lead to increased serum concentrations of risperidone and an increased potential for QT prolongation or other adverse effects. Serious and/or life-threatening drug interactions could potentially occur between atazanavir and risperidone. (Major) Coadministration of risperidone, a CYP2D6 substrate, and cobicistat, a potent CYP2D6 inhibitor, may increase plasma concentrations of risperidone. When oral risperidone is given with a potent CYP2D6 inhibitor, the dose of risperidone should not exceed 8 mg/day PO in adults. When

initiating therapy, titrate risperidone slowly. Upon discontinuation of the CYP2D6 inhibitor, the risperidone dose should be re-evaluated and increased if necessary. For the long-acting risperidone injection, the current adult dosage should be closely monitored when a potent CYP2D6 inhibitor is initiated or discontinued. An adjustment of the dose may be required.

Atenolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of atenolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving atenolol concomitantly.

Atenolol; Chlorthalidone: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of atenolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving atenolol concomitantly.

Atomoxetine: (Major) QT prolongation has occurred during therapeutic use of atomoxetine and following overdose. Atomoxetine is considered a drug with a possible risk of torsade de pointes (TdP). Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with atomoxetine include risperidone.

Atropine; Difenoxin: (Moderate) Concurrent administration of diphenoxylate/difenoxin with risperidone can potentiate the CNS-depressant effects of diphenoxylate/difenoxin. Use caution during coadministration.

Atropine; Diphenoxylate: (Moderate) Concurrent administration of diphenoxylate/difenoxin with risperidone can potentiate the CNS-depressant effects of diphenoxylate/difenoxin. Use caution during coadministration.

Atropine; Hyoscyamine; Phenobarbital; Scopolamine: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.

Azithromycin: (Major) Due to an increased risk for QT prolongation and torsade de pointes (TdP), cautious use of risperidone with azithromycin is advised. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Azithromycin has been associated with post-marketing reports of QT prolongation and TdP. Risperidone has been associated with a possible risk for QT prolongation and/or TdP; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting.

Barbiturates: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.

Bedaquiline: (Major) Due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering bedaquiline with risperidone. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Bedaquiline has been reported to prolong the QT interval. Prior to initiating bedaquiline, obtain serum electrolyte concentrations and a baseline ECG. An ECG should also be performed at least 2, 12, and 24 weeks after starting bedaquiline therapy. Risperidone has also been associated with a possible risk for QT prolongation and/or TdP; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting.

Belladonna Alkaloids; Ergotamine; Phenobarbital: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.

Belladonna; Opium: (Moderate) Additive CNS depression may occur if opiate agonists are used concomitantly with risperidone. The dose of one or both drugs should be reduced.

Bendroflumethiazide; Nadolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of nadolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving nadolol concomitantly.

Benzodiazepines: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.

Benzphetamine: (Major) Concurrent use of antipsychotics and amphetamines should generally be avoided. Antipsychotics and amphetamines may interact pharmacodynamically to diminish the therapeutic effects of either agent through opposing effects on dopamine. Amphetamines are thought to block central dopamine reuptake, which has the potential to exacerbate psychosis, and antipsychotics, which are central dopamine antagonists, may diminish the effectiveness of amphetamines.

Bepridil: (Severe) Bepridil administration is associated with a well-established risk of QT prolongation and

torsades de pointes and is contraindicated in combination with other drugs that may also prolong the QT interval including risperidone.
Betaxolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of betaxolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving betaxolol concomitantly.
Bismuth Subcitrate Potassium; Metronidazole; Tetracycline: (Major) Potential QT prolongation has been reported in limited case reports with metronidazole. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with metronidazole include risperidone.
Bismuth Subsalicylate; Metronidazole; Tetracycline: (Major) Potential QT prolongation has been reported in limited case reports with metronidazole. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with metronidazole include risperidone.
Bisoprolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of bisoprolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving bisoprolol concomitantly.
Bisoprolol; Hydrochlorothiazide, HCTZ: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of bisoprolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving bisoprolol concomitantly.
Boceprevir: (Moderate) Close clinical monitoring is advised when administering risperidone with boceprevir due to an increased potential for risperidone-related adverse events. If risperidone dose adjustments are made, re-adjust the dose upon completion of boceprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of risperidone. Risperidone is a substrate of the drug efflux transporter P-glycoprotein (PGP) and of the hepatic isoenzyme CYP3A4; boceprevir is an inhibitor of both the efflux protein and the isoenzyme. Coadministration may result in elevated risperidone plasma concentrations.
Brexpiprazole: (Major) Caution is advisable during concurrent use of brexpiprazole with other antipsychotics such as risperidone. The risk of drowsiness, dizziness, hypotension, extrapyramidal symptoms, anticholinergic effects, neuroleptic malignant syndrome, or seizures may be increased during combined use; therefore, it may be advisable to initiate treatment with lower dosages if combination therapy is deemed necessary.
Brigatinib: (Moderate) Monitor for decreased efficacy of risperdal if coadministration with brigatinib is necessary; consider increasing the dose of risperdal if clinically indicated. Risperdal is a CYP3A substrate and brigatinib induces CYP3A in vitro; plasma concentrations of risperdal may decrease.
Brimonidine; Timolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of timolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving timolol concomitantly.
Bromocriptine: (Moderate) The prolactin-lowering effect of bromocriptine at the anterior pituitary may be antagonized by medications that increase prolactin levels, such as the atypical antipsychotics. The atypical antipsychotics elevate prolactin to various degrees. Like other drugs that antagonize dopamine D2 receptors, the elevation in prolactin from atypical antipsychotics can persist during chronic administration. Monitor the patient for reduced response to bromocriptine.
Brompheniramine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Brompheniramine; Carbetapentane; Phenylephrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane with other CNS depressants including atypical antipsychotics. (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Brompheniramine; Dextromethorphan; Guaifenesin: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Brompheniramine; Guaifenesin; Hydrocodone: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone. (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Brompheniramine; Hydrocodone; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone. (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Brompheniramine; Pseudoephedrine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Budesonide; Formoterol: (Moderate) Risperidone has been associated with a possible risk for QT

prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Bumetanide: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Buprenorphine: (Major) Due to the potential for QT prolongation and additive CNS depressant effects, cautious use and close monitoring are advisable if concurrent use of risperidone and buprenorphine is necessary. Buprenorphine has been associated with QT prolongation and has a possible risk of torsade de pointes (TdP). Risperidone has a possible risk for QT prolongation and TdP. FDA-approved labeling for some buprenorphine products recommend avoiding use with Class 1A and Class III antiarrhythmic medications while other labels recommend avoiding use with any drug that has the potential to prolong the QT interval. If concurrent use of risperidone and buprenorphine is necessary, consider a dose reduction of one or both drugs. Hypotension, profound sedation, coma, respiratory depression, or death may occur during co-administration of buprenorphine and other CNS depressants. Prior to concurrent use of buprenorphine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Evaluate the patient's use of alcohol or illicit drugs. It is recommended that the injectable buprenorphine dose be halved for patients who receive other drugs with CNS depressant effects; for the buprenorphine transdermal patch, start with the 5 mcg/hour patch. Monitor patients for sedation or respiratory depression.

Buprenorphine; Naloxone: (Major) Due to the potential for QT prolongation and additive CNS depressant effects, cautious use and close monitoring are advisable if concurrent use of risperidone and buprenorphine is necessary. Buprenorphine has been associated with QT prolongation and has a possible risk of torsade de pointes (TdP). Risperidone has a possible risk for QT prolongation and TdP. FDA-approved labeling for some buprenorphine products recommend avoiding use with Class 1A and Class III antiarrhythmic medications while other labels recommend avoiding use with any drug that has the potential to prolong the QT interval. If concurrent use of risperidone and buprenorphine is necessary, consider a dose reduction of one or both drugs. Hypotension, profound sedation, coma, respiratory depression, or death may occur during co-administration of buprenorphine and other CNS depressants. Prior to concurrent use of buprenorphine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Evaluate the patient's use of alcohol or illicit drugs. It is recommended that the injectable buprenorphine dose be halved for patients who receive other drugs with CNS depressant effects; for the buprenorphine transdermal patch, start with the 5 mcg/hour patch. Monitor patients for sedation or respiratory depression.

Bupropion: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as antipsychotics. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored.

Bupropion; Naltrexone: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as antipsychotics. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored.

Buspirone: (Moderate) The combination of buspirone and CNS depressants like the antipsychotics can increase the risk for drowsiness, sedation, and dizziness.

Butabarbital: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.

Butorphanol: (Moderate) Concomitant use of butorphanol with risperidone can potentiate the effects of butorphanol on respiratory depression, CNS depression (e.g., dizziness, impaired mental function), and sedation. Use together with caution. If a centrally acting medication needs to be used with butorphanol, use the smallest effective dose and the longest dosing frequency of butorphanol.

Cabergoline: (Major) Risperidone may inhibit the clinical antiparkinsonian response to cabergoline therapy by blocking dopamine receptors in the brain. In general, atypical antipsychotics like risperidone are less likely to interfere with cabergoline than traditional antipsychotic agents. However, risperidone should be avoided in patients requiring medication for Parkinson's disease unless the benefit of risperidone therapy outweighs the risk of decreased therapeutic response to cabergoline.

Cabozantinib: (Moderate) Monitor for an increase in risperidone-related adverse events if concomitant use with cabozantinib is necessary, as plasma concentrations of risperidone may be increased. Cabozantinib is a P-glycoprotein (P-gp) inhibitor and risperidone is a substrate of P-gp; the clinical relevance of this finding is unknown.

Calcium-channel blockers: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower

dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Canagliflozin: (Moderate) Patients taking canagliflozin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.
Canagliflozin; Metformin: (Moderate) Patients taking canagliflozin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported. (Moderate) Patients taking metformin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.
Carbamazepine: (Major) Coadministration of risperidone and carbamazepine, an enzyme inducer, may decrease plasma concentrations of risperidone. In addition, risperidone may lower the seizure threshold and decrease anticonvulsant efficacy. When oral risperidone is given with an enzyme inducer, slowly titrate the risperidone dose upwards; do not exceed twice the patient's usual dose. Upon discontinuation of the enzyme inducer, the risperidone dose should be re-evaluated and decreased if necessary. For the long-acting injection, adult patients should be closely monitored for the first 4 to 8 weeks after initiation of an enzyme inducer. A dose increase, or additional oral risperidone, may need to be considered. Upon discontinuation of the enzyme inducer, the dosage of injectable risperidone should be re-evaluated and decreased if necessary. Patients may need to be placed on a lower dose of injectable risperidone 2 to 4 weeks before the planned discontinuation of an enzyme inducer to adjust for the expected increase in risperidone plasma concentrations. For patients receiving a 25 mg dose, it is recommended to maintain the 25 mg dose upon discontinuation of the enzyme inducer unless clinical judgment warrants lowering the dose to 12.5 mg or interrupting risperidone treatment. The efficacy of the 12.5 mg dose has not been evaluated in clinical trials.
Carbetapentane; Chlorpheniramine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane with other CNS depressants including atypical antipsychotics. (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Carbetapentane; Chlorpheniramine; Phenylephrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane with other CNS depressants including atypical antipsychotics. (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Carbetapentane; Diphenhydramine; Phenylephrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane with other CNS depressants including atypical antipsychotics. (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as diphenhydramine. This combination is commonly used in clinical practice; however, additive drowsiness or other CNS effects may occur. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Carbetapentane; Guaifenesin: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane with other CNS depressants including atypical antipsychotics.
Carbetapentane; Guaifenesin; Phenylephrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane with other CNS depressants including atypical antipsychotics.
Carbetapentane; Phenylephrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane with other CNS depressants including atypical antipsychotics.
Carbetapentane; Phenylephrine; Pyrilamine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane with other CNS depressants including atypical antipsychotics. (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Carbetapentane; Pseudoephedrine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane with other CNS depressants including atypical antipsychotics.
Carbetapentane; Pyrilamine: (Moderate) Drowsiness has been reported during administration of carbetapentane. An enhanced CNS depressant effect may occur when carbetapentane with other CNS depressants including atypical antipsychotics. (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Carbidopa; Levodopa: (Major) Antipsychotic agents may inhibit the clinical antiparkinsonian response to levodopa by blocking dopamine receptors in the brain. In general, however, the 'atypical antipsychotics' are less likely to interfere with these therapies than traditional antipsychotic agents (e.g., phenothiazines). Antipsychotics should be avoided during therapy for Parkinson's disease unless the benefit of the drug outweighs the risk of

decreased therapeutic response to levodopa or other treatments. In general, experts consider quetiapine the atypical antipsychotic of choice in Parkinson's patients due to a lower incidence of extrapyramidal symptoms, although the choice of antipsychotic medication must always be made on a case-by-case decision.
Carbidopa; Levodopa; Entacapone: (Major) Antipsychotic agents may inhibit the clinical antiparkinsonian response to levodopa by blocking dopamine receptors in the brain. In general, however, the 'atypical antipsychotics' are less likely to interfere with these therapies than traditional antipsychotic agents (e.g., phenothiazines). Antipsychotics should be avoided during therapy for Parkinson's disease unless the benefit of the drug outweighs the risk of decreased therapeutic response to levodopa or other treatments. In general, experts consider quetiapine the atypical antipsychotic of choice in Parkinson's patients due to a lower incidence of extrapyramidal symptoms, although the choice of antipsychotic medication must always be made on a case-by-case decision. (Major) Atypical antipsychotics are central dopamine antagonists and may inhibit the clinical response to antiparkinsonian agents with dopamine agonist properties by blocking dopamine receptors in the brain. Due to the CNS depressant effects of atypical antipsychotics, additive drowsiness may occur with Parkinson's treatments like entacapone or tolcapone. In general, atypical antipsychotics are less likely to interfere with these therapies than traditional antipsychotic agents.
Carbinoxamine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Carbinoxamine; Dextromethorphan; Pseudoephedrine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Carbinoxamine; Hydrocodone; Phenylephrine: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone. (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Carbinoxamine; Hydrocodone; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone. (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Carbinoxamine; Phenylephrine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Carbinoxamine; Pseudoephedrine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Carteolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of carteolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving carteolol concomitantly.
Carvedilol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of carvedilol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving carvedilol concomitantly.
Central-acting adrenergic agents: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Ceritinib: (Major) Periodically monitor electrolytes and ECGs in patients receiving concomitant treatment with ceritinib and risperidone; monitor more closely if the patient has known risk factors for cardiac disease or arrhythmia. An interruption of ceritinib therapy, dose reduction, or discontinuation of therapy may be necessary if QT prolongation occurs. Ceritinib causes concentration-dependent prolongation of the QT interval. Reports of QT prolongation and torsade de pointes (TdP) during risperidone therapy are also noted by the manufacturer, primarily in the overdose setting.
Cetirizine: (Moderate) Additive drowsiness may occur if cetirizine or levocetirizine is administered with other drugs that depress the CNS, such as risperidone. Coadminister these drugs with caution.
Cetirizine; Pseudoephedrine: (Moderate) Additive drowsiness may occur if cetirizine or levocetirizine is administered with other drugs that depress the CNS, such as risperidone. Coadminister these drugs with caution.
Cetrorelix: (Moderate) Antipsychotic-induced hyperprolactinemia results in down-regulation of the number of pituitary GnRH receptors and may interfere with the response to any of the gonadotropin-releasing hormone (GnRH) analogs including cetrorelix.
Chlophedianol; Dexchlorpheniramine; Pseudoephedrine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Chlorcyclizine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when

risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Chlordiazepoxide: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.
Chlordiazepoxide; Clidinium: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.
Chloroquine: (Major) When possible, avoid the coadministration of chloroquine with other drugs known to prolong the QT interval, such as risperidone. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Chloroquine is associated with an increased risk of QT prolongation and TdP; fatalities have been reported. The risk of QT prolongation is increased with higher chloroquine doses. Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes (TdP). Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting.
Chlorpheniramine: (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Chlorpheniramine; Codeine: (Moderate) Concomitant use of codeine with other central nervous system (CNS) depressants, such as risperidone, can potentiate the effects of codeine and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of codeine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of codeine and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Chlorpheniramine; Dextromethorphan: (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Chlorpheniramine; Dihydrocodeine; Phenylephrine: (Moderate) Additive CNS depression may occur if opiate agonists are used concomitantly with risperidone. The dose of one or both drugs should be reduced. (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Chlorpheniramine; Dihydrocodeine; Pseudoephedrine: (Moderate) Additive CNS depression may occur if opiate agonists are used concomitantly with risperidone. The dose of one or both drugs should be reduced. (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Chlorpheniramine; Guaifenesin; Hydrocodone; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone. (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Chlorpheniramine; Hydrocodone: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone. (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.
Chlorpheniramine; Hydrocodone; Phenylephrine: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to

concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone. (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.

Chlorpheniramine; Hydrocodone; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone. (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.

Chlorpheniramine; Phenylephrine: (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.

Chlorpheniramine; Pseudoephedrine: (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as chlorpheniramine. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.

Chlorpromazine: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include chlorpromazine. In addition, coadministration may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.

Cinacalcet: (Major) Coadministration of risperidone, a CYP2D6 substrate, and cinacalcet, a potent CYP2D6 inhibitor, may increase plasma concentrations of risperidone. When oral risperidone is given with a potent CYP2D6 inhibitor, re-evaluate the risperidone dosing and do not exceed risperidone 8 mg/day PO in adults. When initiating therapy, titrate risperidone slowly. Upon discontinuation of the CYP2D6 inhibitor, the risperidone dose should be re-evaluated and increased if necessary. For the long-acting risperidone injection, the current adult dosage should be closely monitored when a potent CYP2D6 inhibitor is initiated or discontinued. An adjustment of the dose may be required.

Ciprofloxacin: (Major) Due to an increased risk for QT prolongation and torsade de pointes (TdP), caution is advised when administering risperidone with ciprofloxacin. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Both risperidone and ciprofloxacin are associated with a possible risk for QT prolongation and TdP; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting.

Cisapride: (Severe) Risperidone has been associated with a possible risk for QT prolongation and torsade de pointes (TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Because of the potential for TdP, use of cisapride with risperidone is contraindicated.

Citalopram: (Major) Because both citalopram and risperidone are associated with a possible risk for QT prolongation and torsade de pointes (TdP), caution is advisable during concurrent use. Citalopram causes dose-dependent QT interval prolongation and risperidone is associated with a risk for QT prolongation and torsade de pointes (TdP). If concurrent therapy is considered essential, ECG monitoring is recommended.

Clarithromycin: (Major) Due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering clarithromycin with risperidone. If coadministration is considered necessary, and the patient has known risk factors for cardiac disease or arrhythmia, then close monitoring is essential. Clarithromycin is associated with an established risk for QT prolongation and TdP. Risperidone has been associated with a possible risk for QT prolongation and/or TdP; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting.

Clemastine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.

Clevidipine: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Clobazam: (Moderate) Clobazam, an inhibitor of CYP2D6, may reduce the metabolism of CYP2D6 substrates, such as aripiprazole, paliperidone, iloperidone, and olanzapine. In addition, benzodiazepines such as clobazam should be combined cautiously with antipsychotics because of the potential for additive CNS depressant effects, and reduced effectiveness of clobazam as an anticonvulsant due to the possible lowering of the seizure threshold by antipsychotics.
Clomipramine: (Moderate) Concurrent use of risperidone and tricyclic antidepressants should be approached with caution. Risperidone has a possible risk for QT prolongation and torsade de pointes and tricyclic antidepressants have rarely been associated with these effects, particularly when given in excessive doses or following overdose. No dosage adjustment of risperidone is recommended based on pharmacokinetic data; however, additive CNS effects are possible.
Clonazepam: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.
Clorazepate: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.
Clozapine: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. In addition, coadministration may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.
Cobicistat: (Major) Coadministration of risperidone, a CYP2D6 substrate, and cobicistat, a potent CYP2D6 inhibitor, may increase plasma concentrations of risperidone. When oral risperidone is given with a potent CYP2D6 inhibitor, the dose of risperidone should not exceed 8 mg/day PO in adults. When initiating therapy, titrate risperidone slowly. Upon discontinuation of the CYP2D6 inhibitor, the risperidone dose should be re-evaluated and increased if necessary. For the long-acting risperidone injection, the current adult dosage should be closely monitored when a potent CYP2D6 inhibitor is initiated or discontinued. An adjustment of the dose may be required.
Cobicistat; Elvitegravir; Emtricitabine; Tenofovir Alafenamide: (Major) Coadministration of risperidone, a CYP2D6 substrate, and cobicistat, a potent CYP2D6 inhibitor, may increase plasma concentrations of risperidone. When oral risperidone is given with a potent CYP2D6 inhibitor, the dose of risperidone should not exceed 8 mg/day PO in adults. When initiating therapy, titrate risperidone slowly. Upon discontinuation of the CYP2D6 inhibitor, the risperidone dose should be re-evaluated and increased if necessary. For the long-acting risperidone injection, the current adult dosage should be closely monitored when a potent CYP2D6 inhibitor is initiated or discontinued. An adjustment of the dose may be required.
Cobicistat; Elvitegravir; Emtricitabine; Tenofovir Disoproxil Fumarate: (Major) Coadministration of risperidone, a CYP2D6 substrate, and cobicistat, a potent CYP2D6 inhibitor, may increase plasma concentrations of risperidone. When oral risperidone is given with a potent CYP2D6 inhibitor, the dose of risperidone should not exceed 8 mg/day PO in adults. When initiating therapy, titrate risperidone slowly. Upon discontinuation of the CYP2D6 inhibitor, the risperidone dose should be re-evaluated and increased if necessary. For the long-acting risperidone injection, the current adult dosage should be closely monitored when a potent CYP2D6 inhibitor is initiated or discontinued. An adjustment of the dose may be required.
Codeine: (Moderate) Concomitant use of codeine with other central nervous system (CNS) depressants, such as risperidone, can potentiate the effects of codeine and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of codeine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of codeine and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
Codeine; Guaifenesin: (Moderate) Concomitant use of codeine with other central nervous system (CNS) depressants, such as risperidone, can potentiate the effects of codeine and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of codeine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of codeine and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
Codeine; Phenylephrine; Promethazine: (Major) Promethazine and risperidone have been associated with a possible risk for QT prolongation and torsade de pointes (TdP) and caution is advisable during coadministration. In addition, because promethazine is a phenothiazine derivative, concurrent use with antipsychotics may increase the risk of drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. Although the incidence of tardive dyskinesia from these combinations has not been established and data are very limited, the risk may be increased during

combined use versus monotherapy. (Moderate) Concomitant use of codeine with other central nervous system (CNS) depressants, such as risperidone, can potentiate the effects of codeine and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of codeine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of codeine and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

Codeine; Promethazine: (Major) Promethazine and risperidone have been associated with a possible risk for QT prolongation and torsade de pointes (TdP) and caution is advisable during coadministration. In addition, because promethazine is a phenothiazine derivative, concurrent use with antipsychotics may increase the risk of drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. Although the incidence of tardive dyskinesia from these combinations has not been established and data are very limited, the risk may be increased during combined use versus monotherapy. (Moderate) Concomitant use of codeine with other central nervous system (CNS) depressants, such as risperidone, can potentiate the effects of codeine and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of codeine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of codeine and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

COMT inhibitors: (Major) Atypical antipsychotics are central dopamine antagonists and may inhibit the clinical response to antiparkinsonian agents with dopamine agonist properties by blocking dopamine receptors in the brain. Due to the CNS depressant effects of atypical antipsychotics, additive drowsiness may occur with Parkinson's treatments like entacapone or tolcapone. In general, atypical antipsychotics are less likely to interfere with these therapies than traditional antipsychotic agents.

Crizotinib: (Major) Monitor ECGs for QT prolongation and monitor electrolytes in patients receiving crizotinib concomitantly with risperidone; the risk is increased in patients with known risk factors for cardiac disease or arrhythmia. An interruption of therapy, dose reduction, or discontinuation of therapy may be necessary for crizotinib patients if QT prolongation occurs. Crizotinib has been associated with concentration-dependent QT prolongation. Risperidone has also been associated with a possible risk for QT prolongation and/or torsade de pointes (TdP), primarily in the overdosage setting.

Cyclizine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.

Cyclobenzaprine: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include cyclobenzaprine.

Cyproheptadine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.

Daclatasvir: (Moderate) Systemic exposure of risperidone, a P-glycoprotein (P-gp) substrate, may be increased when administered concurrently with daclatasvir, a P-gp inhibitor. Taking these drugs together could increase or prolong the therapeutic effects of risperidone; monitor patients for potential adverse effects.

Dantrolene: (Moderate) Simultaneous use of skeletal muscle relaxants and other CNS depressants, such as antipsychotics, can increase CNS depression.

Dapagliflozin: (Moderate) Patients taking dapagliflozin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Dapagliflozin; Metformin: (Moderate) Patients taking dapagliflozin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported. (Moderate) Patients taking metformin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Dapagliflozin; Saxagliptin: (Moderate) Patients taking dapagliflozin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported. (Moderate) Patients taking

saxagliptin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Darunavir: (Major) Decreased risperidone doses may be required when coadministered with darunavir/ritonavir. Darunavir/ritonavir is expected to decrease the hepatic metabolism of the risperidone, resulting in increased risperidone concentrations. If coadministration of these drugs is warranted, do so with caution and careful monitoring.

Darunavir; Cobicistat: (Major) Coadministration of risperidone, a CYP2D6 substrate, and cobicistat, a potent CYP2D6 inhibitor, may increase plasma concentrations of risperidone. When oral risperidone is given with a potent CYP2D6 inhibitor, the dose of risperidone should not exceed 8 mg/day PO in adults. When initiating therapy, titrate risperidone slowly. Upon discontinuation of the CYP2D6 inhibitor, the risperidone dose should be re-evaluated and increased if necessary. For the long-acting risperidone injection, the current adult dosage should be closely monitored when a potent CYP2D6 inhibitor is initiated or discontinued. An adjustment of the dose may be required. (Major) Decreased risperidone doses may be required when coadministered with darunavir/ritonavir. Darunavir/ritonavir is expected to decrease the hepatic metabolism of the risperidone, resulting in increased risperidone concentrations. If coadministration of these drugs is warranted, do so with caution and careful monitoring.

Dasabuvir; Ombitasvir; Paritaprevir; Ritonavir: (Major) Concurrent administration of risperidone with dasabuvir; ombitasvir; paritaprevir; ritonavir or ombitasvir; paritaprevir; ritonavir may result in elevated plasma concentrations of risperidone and ritonavir and increased risk of adverse events. Both ritonavir and risperidone are substrates and inhibitors of the hepatic isoenzyme CYP2D6. In addition, risperidone is a substrate for CYP3A4 and P-glycoprotein (P-gp); ritonavir is a potent CYP3A4 inhibitor and a P-gp inhibitor. Paritaprevir also inhibits P-gp. While dasabuvir; ombitasvir; paritaprevir; ritonavir did not prolong the QTc interval to a clinically relevant extent in healthy subjects, ritonavir has been associated with QT prolongation in other trials. Risperidone has been associated with QT prolongation in post-marketing trials. Concurrent use of risperidone and dasabuvir; ombitasvir; paritaprevir; ritonavir may the increase the risk of QT prolongation. Caution and close monitoring are advised if these drugs are administered together. (Major) If coadministration of risperidone and ritonavir is required, careful monitoring for increased adverse effects of risperidone is recommended. Risperidone is metabolized by CYP3A4, CYP2D6, and P-gp and ritonavir is an inhibitor of CYP3A4, CYP2D6, and P-gp. In addition, both drugs have been associated with QT prolongation, and additive QT effects are possible. A decreased dosage of risperidone may be required.

Dasatinib: (Major) Caution is advised during coadministration of medications with a possible risk for QT prolongation and torsade de pointes (TdP) such as dasatinib and risperidone. If coadministration is necessary and the patient has known risk factors for cardiac disease or arrhythmias, close monitoring is recommended.

Daunorubicin: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsades de pointes; however, data are currently lacking to establish causality in association with torsades de pointes. Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone has potential to prolong the QT interval, it should be used cautiously with daunorubicin due to the potential risks for anthracycline cardiac toxicity. Acute cardiotoxicity can occur during administration of daunorubicin; cumulative, dose-dependent cardiomyopathy may also occur. Acute ECG changes during anthracycline therapy are usually transient and include ST-T wave changes, QT prolongation, and changes in QRS voltage. Sinus tachycardia is the most common arrhythmia, but other arrhythmias such as supraventricular tachycardia (SVT), ventricular tachycardia, heart block, and premature ventricular contractions (PVCs) have been reported during anthracycline therapy.

Degarelix: (Major) Since degarelix can cause QT prolongation, degarelix should be used cautiously, if at all, with other drugs that are associated with QT prolongation like risperidone. In addition, risperidone may cause hyperprolactinemia and should not generally be administered concomitantly with degarelix, as hyperprolactinemia downregulates the number of pituitary gonadotropin-releasing hormone receptors.

Desipramine: (Moderate) Concurrent use of risperidone and tricyclic antidepressants should be approached with caution. Risperidone has a possible risk for QT prolongation and torsade de pointes and tricyclic antidepressants have rarely been associated with these effects, particularly when given in excessive doses or following overdose. No dosage adjustment of risperidone is recommended based on pharmacokinetic data; however, additive CNS effects are possible.

Desvenlafaxine: (Major) Coadministration of risperidone, a CYP2D6 substrate, and desvenlafaxine, a CYP2D6 inhibitor, may increase plasma concentrations of risperidone. Clinical studies have shown desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at doses less than 100 mg/day; hence, per desvenlafaxine product labeling, CYP2D6 substrates can be dosed at the original level when desvenlafaxine doses are 100 mg or less or when desvenlafaxine is discontinued. For desvenlafaxine doses more than 400 mg, product labeling recommends to reduce the risperidone dose by one-half.

Deutetrabenazine: (Major) For patients taking a deutetrabenazine dosage more than 24 mg/day with risperidone, assess the QTc interval before and after increasing the dosage of either medication. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Clinically relevant QTc prolongation may occur with deutetrabenazine. Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes (TdP). Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Monitor for signs and symptoms of neuroleptic malignant syndrome (NMS), restlessness, and agitation. If NMS is diagnosed, immediately discontinue deutetrabenazine, and provide intensive symptomatic treatment and medical monitoring. Recurrence of NMS has been reported with resumption of drug therapy. If akathisia or parkinsonism develops during treatment, the deutetrabenazine dose should be reduced; discontinuation may be required. Deutetrabenazine is a reversible, dopamine depleting drug and risperidone is a dopamine antagonist. The risk for parkinsonism, NMS, or akathisia may be increased with

concomitant administration. Additionally, concurrent use of deutetrabenazine and drugs that can cause CNS depression, such as risperidone, may have additive effects and worsen drowsiness or sedation. Advise patients about worsened somnolence and not to drive or perform other tasks requiring mental alertness until they know how deutetrabenazine affects them.

Dexchlorpheniramine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.

Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.

Dexmethylphenidate: (Moderate) Atypical antipsychotics and dexmethylphenidate may interact pharmacodynamically to diminish the therapeutic effects of either agent through opposing effects on dopamine. Dexmethylphenidate blocks central dopamine reuptake, which has the potential to exacerbate psychosis, and antipsychotics, which are central dopamine antagonists, may diminish the effectiveness of dexmethylphenidate.

Dextroamphetamine: (Major) Concurrent use of antipsychotics and amphetamines should generally be avoided. Antipsychotics and amphetamines may interact pharmacodynamically to diminish the therapeutic effects of either agent through opposing effects on dopamine. Amphetamines are thought to block central dopamine reuptake, which has the potential to exacerbate psychosis, and antipsychotics, which are central dopamine antagonists, may diminish the effectiveness of amphetamines.

Dextromethorphan; Diphenhydramine; Phenylephrine: (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as diphenhydramine. This combination is commonly used in clinical practice; however, additive drowsiness or other CNS effects may occur. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.

Dextromethorphan; Promethazine: (Major) Promethazine and risperidone have been associated with a possible risk for QT prolongation and torsade de pointes (TdP) and caution is advisable during coadministration. In addition, because promethazine is a phenothiazine derivative, concurrent use with antipsychotics may increase the risk of drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. Although the incidence of tardive dyskinesia from these combinations has not been established and data are very limited, the risk may be increased during combined use versus monotherapy.

Dextromethorphan; Quinidine: (Severe) Quinidine administration is associated with QT prolongation and torsades de pointes (TdP). Quinidine inhibits CYP2D6 and has QT-prolonging actions; quinidine is contraindicated with other drugs that prolong the QT interval and are metabolized by CYP2D6 as the effects on the QT interval may be increased during concurrent use of these agents. Drugs that prolong the QT and are substrates for CYP2D6 that are contraindicated with quinidine include risperidone.

Diazepam: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.

Dihydrocodeine; Guaifenesin; Pseudoephedrine: (Moderate) Additive CNS depression may occur if opiate agonists are used concomitantly with risperidone. The dose of one or both drugs should be reduced.

Diltiazem: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Dimenhydrinate: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.

Diphenhydramine: (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as diphenhydramine. This combination is commonly used in clinical practice; however, additive drowsiness or other CNS effects may occur. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.

Diphenhydramine; Hydrocodone; Phenylephrine: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone. (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as diphenhydramine. This combination is commonly used in clinical practice; however, additive drowsiness or other CNS effects may occur. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.

Diphenhydramine; Ibuprofen: (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as diphenhydramine. This combination is commonly used in clinical practice; however, additive drowsiness or other CNS effects may occur. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.

Diphenhydramine; Naproxen: (Moderate) Due to the primary CNS effects of risperidone, caution is advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as diphenhydramine. This combination is commonly used in clinical practice; however, additive drowsiness or other CNS effects may occur. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.

Diphenhydramine; Phenylephrine: (Moderate) Due to the primary CNS effects of risperidone, caution is

advisable when risperidone is given with other centrally acting medications including sedating H1-blockers such as diphenhydramine. This combination is commonly used in clinical practice; however, additive drowsiness or other CNS effects may occur. Patients should be informed of the risk of driving or performing other tasks requiring mental alertness until the effects of these medicines are known.

Disopyramide: (Major) Risperidone should be used cautiously and with close monitoring with disopyramide. Disopyramide administration is associated with QT prolongation and torsades de pointes (TdP). Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically.

Dofetilide: (Severe) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP) Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Dofetilide, a Class III antiarrhythmic agent, is associated with a well-established risk of QT prolongation and TdP. Because of the potential for TdP, use of dofetilide with risperidone is contraindicated.

Dolasetron: (Major) Due to a possible risk for QT prolongation and torsade de pointes (TdP), dolasetron and risperidone should be used together cautiously. Dolasetron has been associated with a dose-dependant prolongation in the QT, PR, and QRS intervals on an electrocardiogram. Use of dolasetron injection for the prevention of chemotherapy-induced nausea and vomiting is contraindicated because the risk of QT prolongation is higher with the doses required for this indication; when the injection is used at lower doses (i.e., those approved for post-operative nausea and vomiting) or when the oral formulation is used, the risk of QT prolongation is lower and caution is advised. Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically.

Dolutegravir; Rilpivirine: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include rilpivirine. Supratherapeutic doses of rilpivirine (75 to 300 mg/day) have caused QT prolongation; caution is advised when administering rilpivirine with other drugs that may prolong the QT or PR interval.

Donepezil: (Major) Case reports indicate that QT prolongation and torsade de pointes (TdP) can occur during donepezil therapy. Donepezil is considered a drug with a known risk of TdP. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with donepezil include risperidone.

Donepezil; Memantine: (Major) Case reports indicate that QT prolongation and torsade de pointes (TdP) can occur during donepezil therapy. Donepezil is considered a drug with a known risk of TdP. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with donepezil include risperidone.

Dopamine: (Minor) The vasoconstrictive properties of dopamine infusion can be decreased due to the alpha-adrenergic blocking capability of risperidone.

Dorzolamide; Timolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of timolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving timolol concomitantly.

Doxazosin: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Doxepin: (Moderate) Concurrent use of risperidone and tricyclic antidepressants should be approached with caution. Risperidone has a possible risk for QT prolongation and torsade de pointes and tricyclic antidepressants have rarely been associated with these effects, particularly when given in excessive doses or following overdose. No dosage adjustment of risperidone is recommended based on pharmacokinetic data; however, additive CNS effects are possible.

Doxorubicin: (Major) Avoid coadministration when possible due to a possible increased risk of QT prolongation and torsade de pointes (TdP). Acute cardiotoxicity can occur during the administration of doxorubicin; although, the incidence is rare. Acute ECG changes during anthracycline therapy are usually transient and include ST-T wave changes, QT prolongation, and changes in QRS voltage. Sinus tachycardia is the most common arrhythmia, but other arrhythmias such as supraventricular tachycardia (SVT), ventricular tachycardia, heart block, and premature ventricular contractions (PVCs) have been reported. Risperidone has a possible risk of causing QT prolongation and TdP.

Doxylamine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.

Doxylamine; Pyridoxine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers.

Additive drowsiness or other CNS effects may occur.
Dronabinol, THC: (Moderate) Drugs that can cause CNS depression such as dronabinol, if used concomitantly with atypical antipsychotics, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness.
Dronedarone: (Severe) Concomitant use of dronedarone with risperidone is contraindicated. Dronedarone is an inhibitor of CYP2D6, CYP3A, and P-gp. Risperidone is a substrate for CYP2D6, CYP3A4, and P-gp. Concomitant use of dronedarone with risperidone may increase risperidone concentrations. In addition, risperidone has been established to have a possible risk of QT prolongation and Torsade de Pointes (TdP). Dronedarone administration is associated with a dose-related increase in the QTc interval. The increase in QTc is approximately 10 milliseconds at doses of 400 mg twice daily (the FDA-approved dose) and up to 25 milliseconds at doses of 1600 mg twice daily. Although there are no studies examining the effects of dronedarone in patients receiving other QT prolonging drugs, coadministration of such drugs may result in additive QT prolongation.
Droperidol: (Major) Droperidol should be administered with extreme caution to patients receiving other agents that may prolong the QT interval. Droperidol administration is associated with an established risk for QT prolongation and torsades de pointes (TdP). Any drug known to have potential to prolong the QT interval should not be coadministered with droperidol. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with droperidol include risperidone. Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically.
Dulaglutide: (Moderate) Patients taking incretin mimetics should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Changes in lipid profiles and weight may also aggravate diabetes or associated conditions or complications. Temporal associations of atypical antipsychotic therapy with the aggravation or new onset of diabetes mellitus have been reported.
Efavirenz: (Major) Coadministration of efavirenz and risperidone may increase the risk for QT prolongation and torsade de pointes (TdP). QT prolongation has been observed with use of efavirenz. Although data are limited, the manufacturer of efavirenz recommends an alternative antiretroviral be considered for patients receiving medications with a known risk for TdP. Risperidone has been associated with a possible risk for QT prolongation and/or TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. In addition, efavirenz may induce the CYP3A4 metabolism of risperidone, potentially reducing the efficacy of risperidone by decreasing its systemic exposure.
Efavirenz; Emtricitabine; Tenofovir: (Major) Coadministration of efavirenz and risperidone may increase the risk for QT prolongation and torsade de pointes (TdP). QT prolongation has been observed with use of efavirenz. Although data are limited, the manufacturer of efavirenz recommends an alternative antiretroviral be considered for patients receiving medications with a known risk for TdP. Risperidone has been associated with a possible risk for QT prolongation and/or TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. In addition, efavirenz may induce the CYP3A4 metabolism of risperidone, potentially reducing the efficacy of risperidone by decreasing its systemic exposure.
Elbasvir; Grazoprevir: (Moderate) Administering risperidone with elbasvir; grazoprevir may result in elevated risperidone plasma concentrations. Risperidone is a substrate of CYP3A; grazoprevir is a weak CYP3A inhibitor. If these drugs are used together, closely monitor for signs of adverse events.
Eliglustat: (Major) Coadministration of risperidone, a CYP2D6 substrate, and eliglustat, a potent CYP2D6 inhibitor, may increase plasma concentrations of risperidone. When oral risperidone is given with a potent CYP2D6 inhibitor, re-evaluate the risperidone dosing and do not exceed risperidone 8 mg/day PO in adults. When initiating therapy, titrate risperidone slowly. Upon discontinuation of the CYP2D6 inhibitor, the risperidone dose should be re-evaluated and increased if necessary. For the long-acting risperidone injection, the current adult dosage should be closely monitored when a potent CYP2D6 inhibitor is initiated or discontinued. An adjustment of the dose may be required.
Empagliflozin: (Moderate) Patients taking empagliflozin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, even diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.
Empagliflozin; Linagliptin: (Moderate) Patients taking empagliflozin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, even diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported. (Moderate) Patients taking linagliptin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.
Empagliflozin; Metformin: (Moderate) Patients taking empagliflozin should be closely monitored for worsening

glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, even diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported. (Moderate) Patients taking metformin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Emtricitabine; Rilpivirine; Tenofovir alafenamide: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include rilpivirine. Supratherapeutic doses of rilpivirine (75 to 300 mg/day) have caused QT prolongation; caution is advised when administering rilpivirine with other drugs that may prolong the QT or PR interval.

Emtricitabine; Rilpivirine; Tenofovir disoproxil fumarate: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include rilpivirine. Supratherapeutic doses of rilpivirine (75 to 300 mg/day) have caused QT prolongation; caution is advised when administering rilpivirine with other drugs that may prolong the QT or PR interval.

Enalapril; Felodipine: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Encainide: (Major) Since risperidone has a possible risk for QT prolongation and torsade de pointes, caution is advisable during concurrent use of other agents also known to have these effects, including encainide.

Entacapone: (Major) Atypical antipsychotics are central dopamine antagonists and may inhibit the clinical response to antiparkinsonian agents with dopamine agonist properties by blocking dopamine receptors in the brain. Due to the CNS depressant effects of atypical antipsychotics, additive drowsiness may occur with Parkinson's treatments like entacapone or tolcapone. In general, atypical antipsychotics are less likely to interfere with these therapies than traditional antipsychotic agents.

Enzalutamide: (Major) The manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer like enzalutamide. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting enzalutamide. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of enzalutamide to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing enzalutamide, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials. Potent inducers of CYP3A4, such as enzalutamide, may decrease plasma concentrations of risperidone and its active metabolite. In an open, randomized two-phase crossover study, another strong CYP3A4 inducer caused significant decreases in risperidone plasma concentrations in healthy volunteers.

Epinephrine: (Major) The alpha-adrenergic effects of epinephrine can be blocked during concurrent administration of risperidone. This blockade can cause an apparently paradoxical condition called 'epinephrine reversal'. The vasoconstrictive properties of dopamine infusion can be decreased due to the alpha-adrenergic blocking capability of risperidone. The use of other agents for vascular support is recommended when needed.

Epirubicin: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsades de pointes; however, data are currently lacking to establish causality in association with torsades de pointes. Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone has potential to prolong the QT interval, it should be used cautiously with daunorubicin, epirubicin, and idarubicin due to the potential risks for anthracycline cardiac toxicity. Acute cardiotoxicity can occur during administration of daunorubicin or doxorubicin; cumulative, dose-dependent cardiomyopathy may also occur. Acute ECG changes during anthracycline therapy are usually transient and include ST-T wave changes, QT prolongation, and changes in QRS voltage. Sinus tachycardia is the most common arrhythmia, but other arrhythmias such as supraventricular tachycardia (SVT), ventricular tachycardia, heart block, and premature ventricular contractions (PVCs) have been reported during anthracycline therapy.

Eplerenone: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Epoprostenol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Eribulin: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de

pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, such as eribulin, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then ECG monitoring is recommended; closely monitor the patient for QT interval prolongation.

Erythromycin: (Major) Concurrent use of risperidone and erythromycin should generally be avoided because risperidone has been associated with a possible risk of QT prolongation and torsade de pointes and erythromycin has a causal association with these effects. In addition, pharmacokinetic data indicate that increased exposure to risperidone and its active metabolite occurs during use of erythromycin. This interaction is thought to be the result of inhibition of CYP3A4, one of the isoenzymes responsible for the metabolism of risperidone.

Erythromycin; Sulfisoxazole: (Major) Concurrent use of risperidone and erythromycin should generally be avoided because risperidone has been associated with a possible risk of QT prolongation and torsade de pointes and erythromycin has a causal association with these effects. In addition, pharmacokinetic data indicate that increased exposure to risperidone and its active metabolite occurs during use of erythromycin. This interaction is thought to be the result of inhibition of CYP3A4, one of the isoenzymes responsible for the metabolism of risperidone.

Escitalopram: (Major) Both risperidone and escitalopram are associated with a possible risk for QT prolongation and torsade de pointes (TdP). If coadministration is necessary, and the patient has known risk factors for cardiac disease or arrhythmias, then closely monitor for QT interval prolongation and adjust the risperidone dosage as needed.

Esmolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of esmolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving esmolol concomitantly.

Estazolam: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.

Eszopiclone: (Moderate) A reduction in the dose of eszopiclone should be considered during co-administration of other CNS depressants, such as antipsychotics, to minimize additive sedative effects. In addition, the risk of next-day psychomotor impairment is increased during co-administration of eszopiclone and other CNS depressants, which may decrease the ability to perform tasks requiring full mental alertness such as driving. Antipsychotics with a higher incidence of sedation, such as olanzapine, clozapine, quetiapine, lurasidone, chlorpromazine, and thioridazine, are more likely to interact with eszopiclone. In one evaluation, concurrent use of eszopiclone and olanzapine reduced psychomotor function as measured by the Digit Symbol Substitution Test (DSST).

Ethacrynic Acid: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Ethanol: (Major) Alcohol is associated with CNS depression. The combined use of alcohol and CNS depressants can lead to additive CNS depression, which could be dangerous in tasks requiring mental alertness and fatal in overdose. Alcohol taken with other CNS depressants can lead to additive respiratory depression, hypotension, profound sedation, or coma. Consider the patient's use of alcohol or illicit drugs when prescribing CNS depressant medications. In many cases, the patient should receive a lower dose of the CNS depressant initially if the patient is not likely to be compliant with avoiding alcohol.

Ethotoin: (Major) Because antipsychotics such as risperidone can lower the seizure threshold, the effectiveness of ethotoin as an anticonvulsant may be reduced. In addition, inducers of CYP3A4, such as ethotoin, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.

Exenatide: (Moderate) Patients taking incretin mimetics should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Changes in lipid profiles and weight may also aggravate diabetes or associated conditions or complications. Temporal associations of atypical antipsychotic therapy with the aggravation or new onset of diabetes mellitus have been reported.

Ezogabine: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include ezogabine.

Felodipine: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Fentanyl: (Moderate) Concomitant use of fentanyl with other central nervous system (CNS) depressants such as risperidone can potentiate the effects of fentanyl and may lead to additive CNS or respiratory depression, profound sedation, or coma. Prior to concurrent use of fentanyl in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If these agents are used together, a reduced dosage of fentanyl and/or the CNS depressant is recommended. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
Fingolimod: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include fingolimod. Fingolimod initiation results in decreased heart rate and may prolong the QT interval. After the first fingolimod dose, overnight monitoring with continuous ECG in a medical facility is advised for patients taking QT prolonging drugs with a known risk of torsades de pointes (TdP). Fingolimod has not been studied in patients treated with drugs that prolong the QT interval, but drugs that prolong the QT interval have been associated with cases of TdP in patients with bradycardia.
Flecainide: (Major) Due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering risperidone with flecainide. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmias, close monitoring is recommended. Risperidone has been associated with a possible risk for QT prolongation and/or TdP, primarily in the overdosage setting. Flecainide, a Class IC antiarrhythmic, increases the QT interval, but largely due to prolongation of the QRS interval. Although causality for TdP has not been established for flecainide, patients receiving concurrent drugs which have the potential for QT prolongation may have an increased risk of developing proarrhythmias.
Fluconazole: (Severe) Fluconazole has been associated with QT prolongation and rare cases of torsades de pointes (TdP). The concurrent use of fluconazole and other drugs that prolong the QT and are CYP3A4 substrates, such as risperidone, is contraindicated due to the risk of life-threatening arrhythmias such as TdP. Coadministration may result in an elevated plasma concentration of risperidone, causing an increased risk for adverse events, such as QT prolongation.
Fluoxetine: (Major) Because QT prolongation and torsade de pointes (TdP) have been reported in patients treated with fluoxetine, the manufacturer recommends caution when using fluoxetine with other drugs that prolong the QT interval. Risperidone is associated with a possible risk of QT prolongation and TdP. In addition, fluoxetine is a potent inhibitor of CYP2D6 and may decrease the clearance of primary CYP2D6 substrates including risperidone. When oral risperidone is given with a CYP2D6 inhibitor, the dose of risperidone should be reduced; do not exceed 8 mg/day PO in adults. When initiating therapy, titrate risperidone slowly. Upon discontinuation of the CYP2D6 inhibitor, the risperidone dose should be re-evaluated and increased if necessary. For the long-acting injection, the current adult dosage should be re-evaluated when a CYP2D6 inhibitor is initiated or discontinued. When initiation of a CYP2D6 inhibitor is considered, patients may be placed on a lower dose of injectable risperidone 2 to 4 weeks prior to initiation to adjust for the expected increase in risperidone plasma concentrations. For patients receiving a 25 mg dose, it is recommended to maintain the 25 mg dose upon initiation of the CYP2D6 inhibitor unless clinical judgment warrants lowering the dose to 12.5 mg or interrupting risperidone therapy. The efficacy of the 12.5 mg dose has not been evaluated in clinical trials. When injectable risperidone is initiated in patients already receiving a CYP2D6 inhibitor, a starting dose of 12.5 mg can be considered. Poor metabolizers of CYP2D6 may also be at greater risk for risperidone-induced adverse events. Decreased metabolism of risperidone may lead to clinically important adverse reactions such as extrapyramidal symptoms. A single case report is noted where the combination of fluoxetine with risperidone induced tardive dyskinesia. Daily doses of fluoxetine 20 mg have been shown to increase risperidone plasma concentrations 2.5- to 2.8-fold. The effects of fluoxetine on the metabolism of interacting drugs may persist for several weeks after discontinuation of fluoxetine because of its long elimination half-life.
Fluoxetine; Olanzapine: (Major) Because QT prolongation and torsade de pointes (TdP) have been reported in patients treated with fluoxetine, the manufacturer recommends caution when using fluoxetine with other drugs that prolong the QT interval. Risperidone is associated with a possible risk of QT prolongation and TdP. In addition, fluoxetine is a potent inhibitor of CYP2D6 and may decrease the clearance of primary CYP2D6 substrates including risperidone. When oral risperidone is given with a CYP2D6 inhibitor, the dose of risperidone should be reduced; do not exceed 8 mg/day PO in adults. When initiating therapy, titrate risperidone slowly. Upon discontinuation of the CYP2D6 inhibitor, the risperidone dose should be re-evaluated and increased if necessary. For the long-acting injection, the current adult dosage should be re-evaluated when a CYP2D6 inhibitor is initiated or discontinued. When initiation of a CYP2D6 inhibitor is considered, patients may be placed on a lower dose of injectable risperidone 2 to 4 weeks prior to initiation to adjust for the expected increase in risperidone plasma concentrations. For patients receiving a 25 mg dose, it is recommended to maintain the 25 mg dose upon initiation of the CYP2D6 inhibitor unless clinical judgment warrants lowering the dose to 12.5 mg or interrupting risperidone therapy. The efficacy of the 12.5 mg dose has not been evaluated in clinical trials. When injectable risperidone is initiated in patients already receiving a CYP2D6 inhibitor, a starting dose of 12.5 mg can be considered. Poor metabolizers of CYP2D6 may also be at greater risk for risperidone-induced adverse events. Decreased metabolism of risperidone may lead to clinically important adverse reactions such as extrapyramidal symptoms. A single case report is noted where the combination of fluoxetine with risperidone induced tardive dyskinesia. Daily doses of fluoxetine 20 mg have been shown to increase risperidone plasma concentrations 2.5- to 2.8-fold. The effects of fluoxetine on the metabolism of interacting drugs may persist for several weeks after discontinuation of fluoxetine because of its long elimination half-life. (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation

and TdP that should be used cautiously with risperidone include olanzapine. Limited data, including some case reports, suggest that olanzapine may be associated with a significant prolongation of the QTc interval in rare instances. In addition, coadministration may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.

Fluphenazine: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation that should be used cautiously with risperidone include fluphenazine. In addition, coadministration may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.

Flurazepam: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.

Fluticasone; Salmeterol: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Fluticasone; Umeclidinium; Vilanterol: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Fluticasone; Vilanterol: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Fluvoxamine: (Major) There may be an increased risk for QT prolongation and torsade de pointes (TdP) during concurrent use of fluvoxamine and risperidone. The benefits versus risks of combined therapy should be assessed, taking into account the patient's underlying disease state(s) and additional potential risk factors. If the patient has known risk factors for cardiac disease or arrhythmias, close monitoring is recommended. Risperidone has been associated with a possible risk for QT prolongation and TdP, primarily in the overdosage setting. Cases of QT prolongation and TdP have been reported during postmarketing use of fluvoxamine.

Food: (Major) It is recommended that patients avoid the use of marijuana, by any route, if they are treated for a psychiatric history, including psychosis and bipolar disorder, as the cannabinoids (the psychoactive ingredients, such as THC) in marijuana can produce psychotoxic effects and may exacerbate psychiatric disorders. A high frequency of use and use of products with high-potency of THC are potential risk factors for psychiatric effects. Additionally, additive CNS effects, such as sedation or CNS depression are possible. Clinical studies suggest that cannabis use may reduce the efficacy of some antipsychotic drugs. In addition, several cannabinoids in marijuana appear to influence the activity of CYP enzymes and P-glycoprotein, which may alter the concentrations of antipsychotics and influence either safety or efficacy, For example, the smoking of marijuana influences the metabolism of some medications in a manner similar to tobacco by inducing CYP1A2.

Formoterol: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely

monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Formoterol; Mometasone: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Fosamprenavir: (Major) Concomitant use of risperidone and fosamprenavir may result in altered risperidone plasma concentrations. Risperidone is a substrate of the hepatic isoenzyme CYP3A4 and drug transporter P-glycoprotein (P-gp). Amprenavir, the active metabolite of fosamprenavir, is an inducer of P-gp and a potent inhibitor and moderate inducer of CYP3A4.

Foscarnet: (Major) When possible, avoid concurrent use of foscarnet with other drugs known to prolong the QT interval, such as risperidone. Foscarnet has been associated with postmarketing reports of both QT prolongation and torsade de pointes (TdP). Risperidone has also been associated with a possible risk for QT prolongation and TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. If these drugs are administered together, obtain an electrocardiogram and electrolyte concentrations before and periodically during treatment.

Fosphenytoin: (Major) Because antipsychotics such as risperidone can lower the seizure threshold, the effectiveness of fosphenytoin may be reduced. In addition, potent inducers of CYP3A4, such as fosphenytoin, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.

Furosemide: (Major) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly. Furthermore, two of four placebo-controlled trials showed that elderly patients with dementia-related psychosis receiving the combination of risperidone and furosemide had a higher incidence of mortality than those receiving either agent alone. The mechanism for this adverse association is unknown. Caution should be exercised when the combined use of risperidone and furosemide is necessary in those with dementia-related psychosis.

Gabapentin: (Moderate) Antipsychotics that may enhance the CNS depressive effects of gabapentin, such as drowsiness or dizziness, include risperidone. Patients should limit activity until they are aware of how coadministration affects them.

Ganirelix: (Moderate) Antipsychotic-induced hyperprolactinemia results in down-regulation of the number of pituitary GnRH receptors and may interfere with the response to ganirelix, a gonadotropin-releasing hormone (GnRH) analog.

Gemifloxacin: (Major) Due to an increased risk for QT prolongation and torsade de pointes (TdP), caution is advised when administering risperidone with gemifloxacin. Risperidone has been associated with a possible risk for QT prolongation and/or TdP; however, data are currently lacking to establish causality in association with TdP. Gemifloxacin may also prolong the QT interval in some patients, with the maximal change in the QTc interval occurring approximately 5 to 10 hours following oral administration. The likelihood of QTc prolongation may increase with increasing dose of gemifloxacin; therefore, the recommended dose should not be exceeded especially in patients with renal or hepatic impairment where the Cmax and AUC are slightly higher.

Gemtuzumab Ozogamicin: (Major) Use gemtuzumab ozogamicin and risperidone together with caution due to the potential for additive QT interval prolongation and risk of torsade de pointes (TdP). If these agents are used together, obtain an ECG and serum electrolytes prior to the start of gemtuzumab and as needed during treatment. Close monitoring is particularly essential for patients with known risk factors for cardiac disease or arrhythmia. Although QT interval prolongation has not been reported with gemtuzumab ozogamicin, it has been reported with other drugs that contain calicheamicin. Risperidone has been associated with a possible risk for QT prolongation and/or TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting.

Glecaprevir; Pibrentasvir: (Moderate) Caution is advised with the coadministration of glecaprevir and risperidone as coadministration may increase serum concentrations of risperidone and increase the risk of adverse effects. Risperidone is a substrate of P-glycoprotein (P-gp); glecaprevir is a P-gp inhibitor. (Moderate) Caution is advised with the coadministration of pibrentasvir and risperidone as coadministration may increase serum concentrations of risperidone and increase the risk of adverse effects. Risperidone is a substrate of P-glycoprotein (P-gp); pibrentasvir is a P-gp inhibitor.

Glimepiride; Pioglitazone: (Moderate) Because risperidone has been associated with hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic states, diabetic coma, and overall worsening of glycemic control, patients taking antidiabetic agents such as thiazolidinediones should be closely monitored for worsening glycemic control when risperidone is instituted. Possible mechanisms for risperidone-related effects on glycemic control include insulin resistance or direct beta-cell inhibition.

Glimepiride; Rosiglitazone: (Moderate) Because risperidone has been associated with hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic states, diabetic coma, and overall worsening of glycemic

control, patients taking antidiabetic agents such as thiazolidinediones should be closely monitored for worsening glycemic control when risperidone is instituted. Possible mechanisms for risperidone-related effects on glycemic control include insulin resistance or direct beta-cell inhibition.

Glipizide; Metformin: (Moderate) Patients taking metformin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Glyburide; Metformin: (Moderate) Patients taking metformin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Glycopyrrolate; Formoterol: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Goserelin: (Moderate) Androgen deprivation therapy (e.g., goserelin) prolongs the QT interval; the risk may be increased with the concurrent use of drugs that may prolong the QT interval. Risperidone is associated with a possible risk for QT prolongation and TdP and should be used cautiously and with close monitoring with goserelin. Additionally, some antipsychotics may induce hyperprolactinemia, resulting in down-regulation of the number of pituitary GnRH receptors and may interfere with the response to goserelin therapy.

Granisetron: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include granisetron.

Guaifenesin; Hydrocodone: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone.

Guaifenesin; Hydrocodone; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone.

Halofantrine: (Severe) Halofantrine is considered to have a well-established risk for QT prolongation and torsades de pointes and should be avoided in patients receiving drugs which may induce QT prolongation including risperidone.

Halogenated Anesthetics: (Major) Halogenated anesthetics should be used cautiously and with close monitoring with risperidone. Halogenated anesthetics can prolong the QT interval. Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors.

Haloperidol: (Major) Caution is advisable when coadministering medications that have a possible risk of QT prolongation and torsade de pointes (TdP), including risperidone and haloperidol. Excessive doses (particularly in the overdose setting) or IV administration of haloperidol may be associated with a higher risk of QT prolongation than with routine oral dosing. Coadministration of haloperidol with risperidone may also increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.

Histrelin: (Moderate) Antipsychotics may cause hyperprolactinemia and should not be administered concomitantly with GnRH analogs since hyperprolactinemia down-regulates the number of pituitary GnRH

receptors.
Homatropine; Hydrocodone: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone.
Hydrochlorothiazide, HCTZ; Metoprolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of metoprolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving metoprolol concomitantly.
Hydrochlorothiazide, HCTZ; Propranolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of propranolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving propranolol concomitantly.
Hydrocodone: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone.
Hydrocodone; Ibuprofen: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone.
Hydrocodone; Phenylephrine: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone.
Hydrocodone; Potassium Guaiacolsulfonate: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone.
Hydrocodone; Potassium Guaiacolsulfonate; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone.
Hydrocodone; Pseudoephedrine: (Moderate) Concomitant use of hydrocodone with other CNS depressants may lead to hypotension, profound sedation, coma, respiratory depression and death. Prior to concurrent use of hydrocodone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Hydrocodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate hydrocodone at 20 to 30% of the usual dosage in patients that are concurrently receiving another CNS depressant. Also consider a using a lower dose of the CNS depressant. Monitor patients for sedation and respiratory depression. Drugs that may cause additive CNS effects include risperidone.
Hydromorphone: (Moderate) Concomitant use of hydromorphone with other central nervous system (CNS) depressants can potentiate the effects of hydromorphone and may lead to additive CNS or respiratory depression, profound sedation, or coma. Examples of drugs associated with CNS depression include risperidone. Prior to concurrent use of hydromorphone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If hydromorphone is used concurrently with a CNS depressant, a reduced dosage of hydromorphone and/or the CNS depressant is recommended; start with one-third to one-half of the estimated hydromorphone starting dose when using hydromorphone extended-release tablets. Carefully monitor the patient for hypotension, CNS depression, and respiratory depression. Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
Hydroxychloroquine: (Major) Ventricular arrhythmias and torsade de pointes (TdP) have been reported with

the use of hydroxychloroquine and coadministration with other drugs having a risk of QT prolongation and TdP, such as risperidone, should be avoided if possible. If coadministration is required and the patient has known risk factors for cardiac disease or arrhythmias, close monitoring is recommended.
Hydroxyzine: (Major) Post-marketing data indicate that hydroxyzine causes QT prolongation and Torsade de Pointes (TdP). Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with hydroxyzine include risperidone. In addition, because hydroxyzine causes pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including risperidone.
Ibuprofen; Oxycodone: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as risperidone, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of oxycodone in patients taking risperidone, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Oxycodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate oxycodone at one-third to one-half the usual dosage in patients that are concurrently receiving another CNS depressant. Also, consider using a lower risperidone dose. Monitor patients for sedation and respiratory depression.
Ibutilide: (Major) Ibutilide administration can cause QT prolongation and torsades de pointes (TdP); proarrhythmic events should be anticipated. The potential for proarrhythmic events with ibutilide increases with the coadministration of other drugs that prolong the QT interval, such as risperidone. Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically.
Idarubicin: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsades de pointes; however, data are currently lacking to establish causality in association with torsades de pointes. Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone has potential to prolong the QT interval, it should be used cautiously with daunorubicin, epirubicin, and idarubicin due to the potential risks for anthracycline cardiac toxicity. Acute cardiotoxicity can occur during administration of daunorubicin or doxorubicin; cumulative, dose-dependent cardiomyopathy may also occur. Acute ECG changes during anthracycline therapy are usually transient and include ST-T wave changes, QT prolongation, and changes in QRS voltage. Sinus tachycardia is the most common arrhythmia, but other arrhythmias such as supraventricular tachycardia (SVT), ventricular tachycardia, heart block, and premature ventricular contractions (PVCs) have been reported during anthracycline therapy.
Iloperidone: (Major) Iloperidone has been associated with QT prolongation; however, torsade de pointes (TdP) has not been reported. According to the manufacturer, since iloperidone may prolong the QT interval, it should be avoided in combination with other agents also known to have this effect, such as risperidone. In addition, coadministration may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.
Imipramine: (Moderate) Concurrent use of risperidone and tricyclic antidepressants should be approached with caution. Risperidone has a possible risk for QT prolongation and torsade de pointes and tricyclic antidepressants have rarely been associated with these effects, particularly when given in excessive doses or following overdose. No dosage adjustment of risperidone is recommended based on pharmacokinetic data; however, additive CNS effects are possible.
Incretin Mimetics: (Moderate) Patients taking incretin mimetics should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Changes in lipid profiles and weight may also aggravate diabetes or associated conditions or complications. Temporal associations of atypical antipsychotic therapy with the aggravation or new onset of diabetes mellitus have been reported.
Indacaterol: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.
Indacaterol; Glycopyrrolate: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be

associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.
Inotuzumab Ozogamicin: (Major) Avoid coadministration of inotuzumab ozogamicin with risperidone due to the potential for additive QT prolongation and risk of torsade de pointes (TdP). If coadministration is unavoidable, obtain an ECG and serum electrolytes prior to the start of treatment, after treatment initiation, and periodically during treatment. Inotuzumab has been associated with QT interval prolongation. Risperidone has been associated with a possible risk for QT prolongation and/or TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting.
Insulin Degludec; Liraglutide: (Moderate) Patients taking incretin mimetics should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Changes in lipid profiles and weight may also aggravate diabetes or associated conditions or complications. Temporal associations of atypical antipsychotic therapy with the aggravation or new onset of diabetes mellitus have been reported.
Insulin Glargine; Lixisenatide: (Moderate) Patients taking incretin mimetics should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Changes in lipid profiles and weight may also aggravate diabetes or associated conditions or complications. Temporal associations of atypical antipsychotic therapy with the aggravation or new onset of diabetes mellitus have been reported.
Insulins: (Moderate) Patients taking insulin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.
Isavuconazonium: (Moderate) Concomitant use of isavuconazonium with risperidone may result in increased serum concentrations of risperidone. Risperidone is a substrate of the hepatic isoenzyme CYP3A4 and drug transporter P-glycoprotein (P-gp); isavuconazole, the active moiety of isavuconazonium, is an inhibitor of CYP3A4 and P-gp. Caution and close monitoring are advised if these drugs are used together.
Isocarboxazid: (Moderate) Due to the potential for additive CNS and cardiovascular effects, MAOIs and antipsychotics should be used together cautiously; some experts recommend initiating low doses of the antipsychotic and careful dosage titration.
Isoniazid, INH; Pyrazinamide, PZA; Rifampin: (Major) The manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer like rifampin. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials. Potent inducers of CYP3A4, such as rifampin, may decrease plasma concentrations of risperidone and its active metabolite. In an open, randomized two-phase crossover study, rifampin caused significant decreases in risperidone plasma concentrations in healthy volunteers.
Isoniazid, INH; Rifampin: (Major) The manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer like rifampin. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials. Potent inducers of CYP3A4, such as rifampin, may decrease plasma concentrations of risperidone and its active metabolite. In an open, randomized two-phase crossover study, rifampin caused significant decreases in risperidone plasma concentrations in healthy volunteers.
Isradipine: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Itraconazole: (Major) Caution is advised when administering itraconazole with risperidone due to the potential for additive effects on the QT interval. Both risperidone and itraconazole are associated with a possible risk for QT prolongation and torsade de pointes (TdP); coadministration may increase this risk.
Ivacaftor: (Minor) Use caution when administering ivacaftor and risperidone concurrently. Ivacaftor is an inhibitor of CYP3A; risperidone is partially metabolized by CYP3A. Co-administration may increase risperidone exposure leading to increased or prolonged therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined.
Kava Kava, Piper methysticum: (Major) Patients who are taking atypical antipsychotics should only use kava kava with prescriber approval and close monitoring. Additive sedation and CNS effects are possible, and inhibition of antipsychotic metabolism may occur. In addition, kava kava has been reported to inhibit many CYP isozymes (i.e., CYP1A2, 2C9, 2C19, 2D6, 3A4, and 4A9/11) and important pharmacokinetic interactions with CNS-active agents that undergo oxidative metabolism via these CYP isozymes are possible. Atypical antipsychotics are metabolized by various CYP isoenzymes and it is not yet documented if pharmacokinetic interactions occur with kava kava. At least 1 case report of a potential clinically significant interaction with kava kava and an atypical antipsychotic has been reported.

Ketoconazole: (Major) Caution is advised when administering ketoconazole with risperidone due to the potential for additive effects on the QT interval. Both risperidone and ketoconazole are associated with a possible risk for QT prolongation and torsade de pointes (TdP); coadministration may increase this risk.
Labetalol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of labetalol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving labetalol concomitantly.
Lapatinib: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include lapatinib. In vitro, lapatinib, at clinically relevant concentrations, inhibits CYP3A4 and CYP2C8. If lapatinib will be coadministered with a CYP3A4 substrate, such as risperidone, exercise extreme caution and consider dose reduction of risperidone.
Ledipasvir; Sofosbuvir: (Moderate) Caution and close monitoring of risperidone-associated adverse reactions is advised with concomitant administration of ledipasvir. Risperidone is a substrate of the drug transporter P-glycoprotein (P-gp); ledipasvir is a P-gp inhibitor. Taking these drugs together may increase risperidone plasma concentrations.
Lenvatinib: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with risperidone include lenvatinib. QT prolongation was reported in patients with radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC) in a double-blind, randomized, placebo-controlled clinical trial after receiving lenvatinib daily at the recommended dose; the QT/QTc interval was not prolonged, however, after a single 32 mg dose (1.3 times the recommended daily dose) in healthy subjects.
Leuprolide: (Major) Androgen deprivation therapy (e.g., leuprolide) prolongs the QT interval; the risk may be increased with the concurrent use of drugs that may prolong the QT interval. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with leuprolide include risperidone.
Leuprolide; Norethindrone: (Major) Androgen deprivation therapy (e.g., leuprolide) prolongs the QT interval; the risk may be increased with the concurrent use of drugs that may prolong the QT interval. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with leuprolide include risperidone.
Levalbuterol: (Minor) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.
Levocetirizine: (Moderate) Additive drowsiness may occur if cetirizine or levocetirizine is administered with other drugs that depress the CNS, such as risperidone. Coadminister these drugs with caution.
Levodopa: (Major) Antipsychotic agents may inhibit the clinical antiparkinsonian response to levodopa by blocking dopamine receptors in the brain. In general, however, the 'atypical antipsychotics' are less likely to interfere with these therapies than traditional antipsychotic agents (e.g., phenothiazines). Antipsychotics should be avoided during therapy for Parkinson's disease unless the benefit of the drug outweighs the risk of decreased therapeutic response to levodopa or other treatments. In general, experts consider quetiapine the atypical antipsychotic of choice in Parkinson's patients due to a lower incidence of extrapyramidal symptoms, although the choice of antipsychotic medication must always be made on a case-by-case decision.
Levofloxacin: (Major) Concurrent use of risperidone and levofloxacin should be avoided due to an increased risk for QT prolongation and torsade de pointes (TdP). Levofloxacin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Additionally, rare cases of TdP have been spontaneously reported during postmarketing surveillance in patients receiving levofloxacin. Risperidone has also been associated with a possible risk for QT prolongation and/or TdP; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting.
Levomethadyl: (Severe) Levomethadyl is associated with an established risk of QT prolongation and/or torsades de pointes and is contraindicated in combination with other agents that may prolong the QT interval, such as risperidone.
Levorphanol: (Moderate) Concomitant use of levorphanol with other CNS depressants such as risperidone can potentiate the effects of levorphanol on respiration, blood pressure, and alertness. Severe hypotension, respiratory depression, profound sedation, or coma may occur. Prior to concurrent use of levorphanol in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. When concomitant treatment with levorphanol with another CNS depressant is necessary, reduce the dose of 1 or both drugs. The initial dose of levorphanol should be reduced by approximately 50% or more when levorphanol is used with another drug that may depress respiration.

Linagliptin: (Moderate) Patients taking linagliptin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.
Linagliptin; Metformin: (Moderate) Patients taking linagliptin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported. (Moderate) Patients taking metformin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.
Liraglutide: (Moderate) Patients taking incretin mimetics should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Changes in lipid profiles and weight may also aggravate diabetes or associated conditions or complications. Temporal associations of atypical antipsychotic therapy with the aggravation or new onset of diabetes mellitus have been reported.
Lisdexamfetamine: (Major) Concurrent use of antipsychotics and amphetamines should generally be avoided. Antipsychotics and amphetamines may interact pharmacodynamically to diminish the therapeutic effects of either agent through opposing effects on dopamine. Amphetamines are thought to block central dopamine reuptake, which has the potential to exacerbate psychosis, and antipsychotics, which are central dopamine antagonists, may diminish the effectiveness of amphetamines.
Lithium: (Major) Because risperidone and lithium are associated with QT prolongation, coadministration may increase the risk of QT prolongation. In addition, it is advisable to monitor patients for neurotoxicity. Neuroleptic malignant syndrome (NMS) has been observed occasionally during concurrent use of lithium and either atypical or conventional antipsychotics. Additive extrapyramidal effects have also been noted. Early case reports described an encephalopathic syndrome consisting of delirium, tremulousness, dyskinesia, seizures, leukocytosis, weakness, hyperpyrexia, confusion, extrapyramidal symptoms, elevations in laboratory values (e.g., liver function tests, blood urea nitrogen, fasting blood sugar) and, in some cases, irreversible brain damage, during use of lithium and conventional antipsychotics, particularly haloperidol. Subsequent rare reports of NMS or NMS-like reactions have been described during coadministration of lithium and atypical antipsychotics. Following resolution of NMS, there are isolated instances of re-emergence of symptoms following re-initiation of lithium as monotherapy. Lithium may be a risk factor for antipsychotic-induced NMS; however, this hypothesis has not been confirmed. In many reported cases, confounding factors have been present (e.g., previous history of NMS, high dose therapy). The ability of antipsychotics alone to precipitate NMS and the rarity of the condition further complicate assessment of lithium as a risk factor. Risperidone has not been shown to alter the AUC or Cmax of lithium.
Lixisenatide: (Moderate) Patients taking incretin mimetics should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Changes in lipid profiles and weight may also aggravate diabetes or associated conditions or complications. Temporal associations of atypical antipsychotic therapy with the aggravation or new onset of diabetes mellitus have been reported.
Lomefloxacin: (Moderate) Quinolones have been associated with QT prolongation and in rare cases, torsades de pointes and should be used with caution in patients receiving drugs that prolong the QT interval, such as risperidone.
Long-acting beta-agonists: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.
Loperamide: (Major) Both loperamide and risperidone are associated with a possible risk for QT prolongation and torsade de pointes (TdP) and should be coadministered with caution and close monitoring. Reports of QT prolongation and TdP during risperidone therapy have occurred primarily in the overdosage setting. At high doses, loperamide has been associated with serious cardiac toxicities, including syncope, ventricular tachycardia, QT prolongation, TdP, and cardiac arrest.
Loperamide; Simethicone: (Major) Both loperamide and risperidone are associated with a possible risk for QT prolongation and torsade de pointes (TdP) and should be coadministered with caution and close monitoring. Reports of QT prolongation and TdP during risperidone therapy have occurred primarily in the overdosage setting. At high doses, loperamide has been associated with serious cardiac toxicities, including syncope, ventricular tachycardia, QT prolongation, TdP, and cardiac arrest.
Lopinavir; Ritonavir: (Major) If coadministration of risperidone and ritonavir is required, careful monitoring for increased adverse effects of risperidone is recommended. Risperidone is metabolized by CYP3A4, CYP2D6,

and P-gp and ritonavir is an inhibitor of CYP3A4, CYP2D6, and P-gp. In addition, both drugs have been associated with QT prolongation, and additive QT effects are possible. A decreased dosage of risperidone may be required. (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include lopinavir; ritonavir. In addition, lopinavir; ritonavir inhibits CYP3A4 metabolism. Coadministration with drugs that are substrates of CYP3A4, such as risperidone, may result in elevated plasma concentrations of risperidone.

Loratadine: (Minor) Although loratadine is considered a 'non-sedating' antihistamine, dose-related sedation has been noted. For this reason, it would be prudent to monitor for drowsiness when used concurrently with other CNS depressants such as antipsychotics.

Loratadine; Pseudoephedrine: (Minor) Although loratadine is considered a 'non-sedating' antihistamine, dose-related sedation has been noted. For this reason, it would be prudent to monitor for drowsiness when used concurrently with other CNS depressants such as antipsychotics.

Lorazepam: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.

Loxapine: (Major) Caution is advisable during concurrent use of loxapine and risperidone. Loxapine use has been associated with adverse events such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, and seizures. These effects may be potentiated during concurrent use of loxapine and risperidone. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.

Lumacaftor; Ivacaftor: (Minor) Use caution when administering ivacaftor and risperidone concurrently. Ivacaftor is an inhibitor of CYP3A; risperidone is partially metabolized by CYP3A. Co-administration may increase risperidone exposure leading to increased or prolonged therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined.

Lurasidone: (Major) Co-administration of risperidone with lurasidone may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.

Maprotiline: (Major) Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect. Medications known to prolong the QT interval include certain heterocyclic antidepressants (e.g., maprotiline), particularly during overdose. In addition, increased maprotiline concentrations have been reported during the coadministration of risperidone, some patients have reported increased anticholinergic side effects in the absence of significant cardiac toxicity. Monitor patients receiving maprotiline concurrently with risperidone for side effects.

Meclizine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including meclizine. Additive drowsiness or other CNS effects may occur.

Mefloquine: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include mefloquine.

Meglitinides: (Moderate) Patients taking meglitinides should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Meperidine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including meperidine. Hypotension, respiratory and/or CNS depression can be additive if meperidine is used concomitantly with risperidone.

Meperidine; Promethazine: (Major) Promethazine and risperidone have been associated with a possible risk for QT prolongation and torsade de pointes (TdP) and caution is advisable during coadministration. In addition, because promethazine is a phenothiazine derivative, concurrent use with antipsychotics may increase the risk of drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. Although the incidence of tardive dyskinesia from these combinations has not been established and data are very limited, the risk may be increased during combined use versus monotherapy. (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including meperidine. Hypotension, respiratory and/or CNS depression can be additive if meperidine is used concomitantly with risperidone.

Mephobarbital: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8

weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.

Meprobamate: (Moderate) The CNS-depressant effects of meprobamate can be potentiated with concomitant administration of other drugs known to cause CNS depression including antipsychotics.

Mesoridazine: (Severe) Due to the risk of additive QT prolongation and potential for serious arrhythmias, the concurrent use of risperidone and mesoridazine is considered contraindicated. Mesoridazine has an established risk of QT prolongation and torsade de pointes (TdP) and risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes (TdP), primarily in the setting of overdose.

Metaproterenol: (Minor) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Metformin: (Moderate) Patients taking metformin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Metformin; Pioglitazone: (Moderate) Because risperidone has been associated with hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic states, diabetic coma, and overall worsening of glycemic control, patients taking antidiabetic agents such as thiazolidinediones should be closely monitored for worsening glycemic control when risperidone is instituted. Possible mechanisms for risperidone-related effects on glycemic control include insulin resistance or direct beta-cell inhibition. (Moderate) Patients taking metformin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Metformin; Repaglinide: (Moderate) Patients taking meglitinides should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported. (Moderate) Patients taking metformin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Metformin; Rosiglitazone: (Moderate) Because risperidone has been associated with hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic states, diabetic coma, and overall worsening of glycemic control, patients taking antidiabetic agents such as thiazolidinediones should be closely monitored for worsening glycemic control when risperidone is instituted. Possible mechanisms for risperidone-related effects on glycemic control include insulin resistance or direct beta-cell inhibition. (Moderate) Patients taking metformin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Metformin; Saxagliptin: (Moderate) Patients taking metformin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported. (Moderate) Patients taking saxagliptin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Metformin; Sitagliptin: (Moderate) Patients taking metformin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. Temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported. (Moderate) Patients taking sitagliptin should be closely monitored for worsening

glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Methadone: (Major) Methadone has a known risk of QT prolongation and torsade de pointes (TdP) and a careful assessment of risks versus benefits should be performed before coadministration with drugs having a possible risk of QT prolongation and TdP such as risperidone. Methadone is particularly associated with an increased risk for QT prolongation and TdP at higher doses (e.g., 400 mg/day in adults). Concomitant use of CNS depressants, such as risperidone and methadone, can lead to additive CNS depression, hypotension, or coma. Prior to the use of methadone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, the patient's overall response to treatment, and the patient's use of alcohol or illicit drugs. In opioid-naive adults, initiate methadone at a dose of 2.5 mg every 12 hours in patients receiving other CNS depressants. Also consider using a lower dose of the CNS depressant.

Methamphetamine: (Major) Concurrent use of antipsychotics and amphetamines should generally be avoided. Antipsychotics and amphetamines may interact pharmacodynamically to diminish the therapeutic effects of either agent through opposing effects on dopamine. Amphetamines are thought to block central dopamine reuptake, which has the potential to exacerbate psychosis, and antipsychotics, which are central dopamine antagonists, may diminish the effectiveness of amphetamines.

Methohexital: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.

Methylphenidate: (Moderate) Atypical antipsychotics and methylphenidate may interact pharmacodynamically to diminish the therapeutic effects of either agent through opposing effects on dopamine. Methylphenidate blocks central dopamine reuptake, which has the potential to exacerbate psychosis, and antipsychotics, which are central dopamine antagonists, may diminish the effectiveness of methylphenidate.

Metoclopramide: (Severe) Concomitant use of metoclopramide and antipsychotics is contraindicated by the manufacturer of metoclopramide as the risk of extrapyramidal effects may be increased. Both metoclopramide and antipsychotics antagonize dopamine receptors, which can increase the risk of extrapyramidal effects, including tardive dyskinesia or other dystonic reactions. Additionally, because both antipsychotics and metoclopramide can cause sedation, seizures, or increased prolactin levels, it is possible that the risk of these effects may be increased during concurrent use.

Metoprolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of metoprolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving metoprolol concomitantly.

Metronidazole: (Major) Potential QT prolongation has been reported in limited case reports with metronidazole. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with metronidazole include risperidone.

Metyrapone: (Moderate) Metyrapone may cause dizziness and/or drowsiness. Other drugs that may also cause drowsiness, such as risperidone, should be used with caution. Additive drowsiness and/or dizziness is possible.

Midazolam: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.

Midostaurin: (Major) The concomitant use of midostaurin and risperidone may lead to additive QT interval prolongation. If these drugs are used together, consider electrocardiogram (ECG) monitoring. In clinical trials, QT prolongation has been reported in patients who received midostaurin as single-agent therapy or in combination with cytarabine and daunorubicin. Pooled data from controlled trials indicate there are no statistically significant differences in mean changes from baseline in ECG parameters including QT, QTc, and PR intervals when risperidone is compared to placebo. However, post-marketing reports of overdose indicate that QT prolongation and torsade de pointes have occurred.

Mifepristone, RU-486: (Major) Due to a possible risk for QT prolongation and torsade de pointes (TdP), mifepristone and risperidone should be used together cautiously. Mifepristone has been associated with dose-dependent prolongation of the QT interval. There is no experience with high exposure or concomitant use with other QT prolonging drugs. To minimize the risk of QT prolongation, the lowest effective dose should always be used. Risperidone has been associated with a possible risk for QT prolongation and TdP; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically.

Miglitol: (Moderate) Patients taking alpha-glucosidase inhibitors should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Mirtazapine: (Major) There may be an increased risk for QT prolongation and torsade de pointes (TdP) during concurrent use of mirtazapine and risperidone. The benefits versus risks of combined therapy should be assessed, taking into account the patient's underlying disease state(s) and additional potential risk factors. If the

patient has known risk factors for cardiac disease or arrhythmias, close monitoring is recommended. Risperidone has been associated with a possible risk for QT prolongation and TdP, primarily in the overdosage setting. Cases of QT prolongation, TdP, ventricular tachycardia, and sudden death have been reported during postmarketing use of mirtazapine, primarily following overdose or in patients with other risk factors for QT prolongation, including concomitant use of other medications associated with QT prolongation.

Mitotane: (Major) The manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer like mitotane. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting mitotane. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of mitotane to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing mitotane, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials. Potent inducers of CYP3A4, such as mitotane, may decrease plasma concentrations of risperidone and its active metabolite. In an open, randomized two-phase crossover study, another strong CYP3A4 inducer caused significant decreases in risperidone plasma concentrations in healthy volunteers.

Molindone: (Major) Co-administration of risperidone with molindone may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.

Monoamine oxidase inhibitors: (Moderate) Due to the potential for additive CNS and cardiovascular effects, MAOIs and antipsychotics should be used together cautiously; some experts recommend initiating low doses of the antipsychotic and careful dosage titration.

Morphine: (Moderate) Concomitant use of morphine with other CNS depressants can potentiate the effects of morphine on respiration, blood pressure, and alertness; examples of other CNS depressants include risperidone. Prior to concurrent use of morphine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with morphine, a reduced dosage of morphine and/or the CNS depressant is recommended; for extended-release products, start with the lowest possible dose of morphine (i.e., 15 mg PO every 12 hours, extended-release tablets; 30 mg or less PO every 24 hours, extended-release capsules). Monitor patients for sedation and respiratory depression.

Morphine; Naltrexone: (Moderate) Concomitant use of morphine with other CNS depressants can potentiate the effects of morphine on respiration, blood pressure, and alertness; examples of other CNS depressants include risperidone. Prior to concurrent use of morphine in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with morphine, a reduced dosage of morphine and/or the CNS depressant is recommended; for extended-release products, start with the lowest possible dose of morphine (i.e., 15 mg PO every 12 hours, extended-release tablets; 30 mg or less PO every 24 hours, extended-release capsules). Monitor patients for sedation and respiratory depression.

Moxifloxacin: (Major) Concurrent use of risperidone and moxifloxacin should be avoided due to an increased risk for QT prolongation and torsade de pointes (TdP). If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Moxifloxacin has been associated with prolongation of the QT interval. Additionally, post-marketing surveillance has identified very rare cases of ventricular arrhythmias including TdP, usually in patients with severe underlying proarrhythmic conditions. The likelihood of QT prolongation may increase with increasing concentrations of moxifloxacin, therefore the recommended dose or infusion rate should not be exceeded. Risperidone has also been associated with a possible risk for QT prolongation and/or TdP; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting.

Nabilone: (Moderate) Drugs that can cause CNS depression, if used concomitantly with atypical antipsychotics, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness.

Nadolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of nadolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving nadolol concomitantly.

Nafarelin: (Moderate) Antipsychotics may cause hyperprolactinemia and should not be administered concomitantly with nafarelin since hyperprolactinemia down-regulates the number of pituitary GnRH receptors.

Nalbuphine: (Moderate) Drugs that can cause CNS depression such as nalbuphine, if used concomitantly with atypical antipsychotics, can increase both the frequency and the intensity of adverse effects such as drowsiness, sedation, and dizziness.

Nateglinide: (Moderate) Patients taking meglitinides should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Nebivolol: (Moderate) Risperidone may cause orthostatic hypotension and thus enhance the hypotensive effects of nebivolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving nebivolol.

Nebivolol; Valsartan: (Moderate) Risperidone may cause orthostatic hypotension and thus enhance the hypotensive effects of nebivolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving nebivolol.

Nicardipine: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the

hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Nifedipine: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Nilotinib: (Major) If possible, avoid the concomitant use of nilotinib with other agents that may cause QT prolongation and torsade de pointes (TdP), such as risperidone. If coadministration is required and the patient has risk factors for cardiac disease or arrhythmias, careful monitoring is recommended.
Nimodipine: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Nisoldipine: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Non-Ionic Contrast Media: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Antipsychotics should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Norfloxacin: (Major) Due to an increased risk for QT prolongation and torsade de pointes (TdP), caution is advised when administering risperidone with norfloxacin. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Quinolones have been associated with QT prolongation and TdP. For norfloxacin specifically, extremely rare cases of TdP were reported during post-marketing surveillance. These reports generally involved patients with concurrent medical conditions or concomitant medications that may have been contributory. Risperidone has also been associated with a possible risk for QT prolongation and/or TdP; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting.
Nortriptyline: (Moderate) Concurrent use of risperidone and tricyclic antidepressants should be approached with caution. Risperidone has a possible risk for QT prolongation and torsade de pointes and tricyclic antidepressants have rarely been associated with these effects, particularly when given in excessive doses or following overdose. No dosage adjustment of risperidone is recommended based on pharmacokinetic data; however, additive CNS effects are possible.
Octreotide: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include octreotide. Arrhythmias, sinus bradycardia, and conduction disturbances have occurred during octreotide therapy warranting more cautious monitoring during octreotide administration in higher risk patients with cardiac disease. Since bradycardia is a risk factor for development of TdP, the potential occurrence of bradycardia during octreotide administration could theoretically increase the risk of TdP in patients receiving drugs that prolong the QT interval.
Ofloxacin: (Major) Due to an increased risk for QT prolongation and torsade de pointes (TdP), caution is advised when administering risperidone with ofloxacin. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Some quinolones, including ofloxacin, have also been associated with QT prolongation. Additionally, post-marketing surveillance for ofloxacin has identified very rare cases of TdP.
Olanzapine: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include olanzapine. Limited data, including some case reports, suggest that olanzapine may be associated with a significant prolongation of the QTc interval in rare instances. In addition, coadministration may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.
Olodaterol: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account

the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Ombitasvir; Paritaprevir; Ritonavir: (Major) Concurrent administration of risperidone with dasabuvir; ombitasvir; paritaprevir; ritonavir or ombitasvir; paritaprevir; ritonavir may result in elevated plasma concentrations of risperidone and ritonavir and increased risk of adverse events. Both ritonavir and risperidone are substrates and inhibitors of the hepatic isoenzyme CYP2D6. In addition, risperidone is a substrate for CYP3A4 and P-glycoprotein (P-gp); ritonavir is a potent CYP3A4 inhibitor and a P-gp inhibitor. Paritaprevir also inhibits P-gp. While dasabuvir; ombitasvir; paritaprevir; ritonavir did not prolong the QTc interval to a clinically relevant extent in healthy subjects, ritonavir has been associated with QT prolongation in other trials. Risperidone has been associated with QT prolongation in post-marketing trials. Concurrent use of risperidone and dasabuvir; ombitasvir; paritaprevir; ritonavir may the increase the risk of QT prolongation. Caution and close monitoring are advised if these drugs are administered together. (Major) If coadministration of risperidone and ritonavir is required, careful monitoring for increased adverse effects of risperidone is recommended. Risperidone is metabolized by CYP3A4, CYP2D6, and P-gp and ritonavir is an inhibitor of CYP3A4, CYP2D6, and P-gp. In addition, both drugs have been associated with QT prolongation, and additive QT effects are possible. A decreased dosage of risperidone may be required.

Ondansetron: (Major) Due to a possible risk for QT prolongation and torsade de pointes (TdP) with both ondansetron and risperidone, coadministration should be avoided if possible. If ondansetron and another drug that prolongs the QT interval must be coadministered, ECG monitoring is recommended. Among 42 patients receiving a 4 mg bolus dose of intravenous ondansetron for the treatment of postoperative nausea and vomiting, the mean maximal QTc interval prolongation was 20 +/- 13 msec at the third minute after antiemetic administration. There are reports of QT prolongation and torsade de pointes during risperidone therapy, primarily in the setting of overdosage.

Osimertinib: (Major) Monitor electrolytes and ECGs for QT prolongation if coadministration of risperidone with osimertinib is necessary; an interruption of osimertinib therapy and dose reduction may be necessary if QT prolongation occurs. Concentration-dependent QTc prolongation occurred during clinical trials of osimertinib. Risperidone has also been associated with a possible risk for QT prolongation and/or torsade de pointes (TdP), primarily in the overdose setting.

Oxaliplatin: (Major) Closely monitor electrolytes and ECGs for QT prolongation if coadministration of risperidone with oxaliplatin is necessary; correct electrolyte abnormalities prior to administration of oxaliplatin. Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes (TdP), primarily in the overdose setting. QT prolongation and ventricular arrhythmias including fatal TdP have also been reported with oxaliplatin use in postmarketing experience.

Oxazepam: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.

Oxycodone: (Moderate) Concomitant use of oxycodone with other CNS depressants, such as risperidone, can lead to additive respiratory depression, hypotension, profound sedation, or coma. Prior to concurrent use of oxycodone in patients taking risperidone, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. Oxycodone should be used in reduced dosages if used concurrently with a CNS depressant; initiate oxycodone at one-third to one-half the usual dosage in patients that are concurrently receiving another CNS depressant. Also, consider using a lower risperidone dose. Monitor patients for sedation and respiratory depression.

Oxymorphone: (Moderate) Concomitant use of oxymorphone with other CNS depressants may produce additive CNS depressant effects. Hypotension, profound sedation, coma, respiratory depression, or death may occur; examples of other CNS depressants include risperidone. Prior to concurrent use of oxymorphone in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with oxymorphone, a reduced dosage of oxymorphone (1/3 to 1/2 of the usual dose) and/or the CNS depressant is recommended. If the extended-release oxymorphone tablets are used concurrently with a CNS depressant, it is recommended to use an initial dosage of 5 mg PO every 12 hours. Monitor for sedation or respiratory depression.

Paliperidone: (Major) Paliperidone has been associated with QT prolongation; however, torsade de pointes (TdP) has not been reported. According to the manufacturer, since paliperidone may prolong the QT interval, it should be avoided in combination with other agents also known to have this effect, such as risperidone. In addition, coadministration may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone. It should be noted that since paliperidone is the major active metabolite of risperidone, excessive paliperidone exposure is possible during concurrent use of the two drugs. If coadministration is considered necessary by the practitioner, and the patient has known risk factors for cardiac disease or arrhythmia, then close monitoring is essential.

Panobinostat: (Major) The coadministration of panobinostat with risperidone should be avoided if possible; both agents have a possible risk for QT prolongation and torsade de pointes. If coadministration is necessary and the patient has known risk factors for cardiac disease or arrhythmias, close monitoring is recommended.

Paroxetine: (Major) Risperidone is associated with a risk for QT prolongation and torsade de pointes, and should be used cautiously with potent CYP2D6 inhibitors such as paroxetine. Paroxetine may decrease the clearance of CYP2D6 substrates such as risperidone. When oral risperidone is given with a CYP2D6 inhibitor, the dose of risperidone should be reduced; do not exceed 8 mg/day PO in adults. When initiating therapy, titrate risperidone slowly. Upon discontinuation of the CYP2D6 inhibitor, the risperidone dose should be re-evaluated

and increased if necessary. For the long-acting injection, the current adult dosage should be re-evaluated when a CYP2D6 inhibitor is initiated or discontinued. When initiation of a CYP2D6 inhibitor is considered, patients may be placed on a lower dose of injectable risperidone 2 to 4 weeks prior to initiation to adjust for the expected increase in risperidone plasma concentrations. For patients receiving a 25 mg dose, it is recommended to maintain the 25 mg dose upon initiation of the CYP2D6 inhibitor unless clinical judgment warrants lowering the dose to 12.5 mg or interrupting risperidone therapy. The efficacy of the 12.5 mg dose has not been evaluated in clinical trials. When injectable risperidone is initiated in patients already receiving a CYP2D6 inhibitor, a starting dose of 12.5 mg can be considered. Poor metabolizers of CYP2D6 may also be at greater risk for risperidone-induced adverse events. Decreased metabolism of risperidone may lead to clinically important adverse reactions that are associated with antipsychotic use, such as extrapyramidal symptoms. Daily dosing of paroxetine 20 mg PO in patients stabilized on risperidone (4 to 8 mg/day) increased mean plasma concentrations of risperidone roughly 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. Other data suggest that daily administration of paroxetine increases plasma concentrations of risperidone 3- to 9-fold.

Pasireotide: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, such as pasireotide. Consider the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically.

Pazopanib: (Major) Both risperidone and pazopanib have been associated with a possible risk for QT prolongation and torsade de pointes; therefore, caution is advisable during coadministration. If concurrent treatment is required and the patient has risk factors for cardiac disease or arrhythmias, close monitoring is recommended.

Penbutolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of penbutolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving penbutolol concomitantly.

Pentamidine: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include pentamidine.

Pentazocine: (Moderate) Coadministration of pentazocine with atypical antipsychotics may result in additive respiratory and CNS depression and anticholinergic effects, such as urinary retention and constipation. Use pentazocine with caution in any patient receiving medication with CNS depressant and/or anticholinergic activity.

Pentazocine; Naloxone: (Moderate) Coadministration of pentazocine with atypical antipsychotics may result in additive respiratory and CNS depression and anticholinergic effects, such as urinary retention and constipation. Use pentazocine with caution in any patient receiving medication with CNS depressant and/or anticholinergic activity.

Pentobarbital: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.

Perampanel: (Moderate) Co-administration of perampanel with CNS depressants, including ethanol, may increase CNS depression. The combination of perampanel (particularly at high doses) with ethanol has led to decreased mental alertness and ability to perform complex tasks (such as driving), as well as increased levels of anger, confusion, and depression; similar reactions should be expected with concomitant use of other CNS depressants, such as risperidone.

Pergolide: (Major) Pergolide is a potent dopamine-receptor agonist. Antipsychotic agents may inhibit the clinical antiparkinsonian response to pergolide by blocking dopamine receptors in the brain. In general, the atypical antipsychotics are less likely to interfere with antiparkinsons treatments than traditional antipsychotic agents. However, antipsychotics should be avoided during therapy for Parkinson's disease unless the benefit of the drug outweighs the risk of decreased therapeutic response to pergolide.

Perindopril; Amlodipine: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Perphenazine: (Moderate) Perphenazine, a phenothiazine, is associated with a possible risk for QT prolongation. Theoretically, perphenazine may increase the risk of QT prolongation if coadministered with drugs with a possible risk for QT prolongation, such as risperidone. Co-administration of perphenazine with atypical agents (e.g., lurasidone and others) may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent. Although the incidence of tardive dyskinesia from combination

antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.
Perphenazine; Amitriptyline: (Moderate) Concurrent use of risperidone and tricyclic antidepressants should be approached with caution. Risperidone has a possible risk for QT prolongation and torsade de pointes and tricyclic antidepressants have rarely been associated with these effects, particularly when given in excessive doses or following overdose. No dosage adjustment of risperidone is recommended based on pharmacokinetic data; however, additive CNS effects are possible. (Moderate) Perphenazine, a phenothiazine, is associated with a possible risk for QT prolongation. Theoretically, perphenazine may increase the risk of QT prolongation if coadministered with drugs with a possible risk for QT prolongation, such as risperidone. Co-administration of perphenazine with atypical agents (e.g., lurasidone and others) may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.
Phenelzine: (Moderate) Due to the potential for additive CNS and cardiovascular effects, MAOIs and antipsychotics should be used together cautiously; some experts recommend initiating low doses of the antipsychotic and careful dosage titration.
Phenobarbital: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.
Phenoxybenzamine: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Phentolamine: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Phenylephrine; Promethazine: (Major) Promethazine and risperidone have been associated with a possible risk for QT prolongation and torsade de pointes (TdP) and caution is advisable during coadministration. In addition, because promethazine is a phenothiazine derivative, concurrent use with antipsychotics may increase the risk of drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. Although the incidence of tardive dyskinesia from these combinations has not been established and data are very limited, the risk may be increased during combined use versus monotherapy.
Phenytoin: (Major) Because antipsychotics such as risperidone can lower the seizure threshold, the effectiveness of phenytoin as an anticonvulsant may be reduced. In addition, potent inducers of CYP3A4, such as phenytoin, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.
Pimavanserin: (Major) Pimavanserin may cause QT prolongation and should generally be avoided in patients receiving other medications known to prolong the QT interval. Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Consider the patient's underlying disease state(s) and additional potential risk factors if pimavanserin and risperidone coadministration cannot be avoided. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically.
Pimozide: (Severe) Risperidone has a risk of QT prolongation and is contraindicated with pimozide. Concurrent use of pimozide with atypical agents may increase the risk of adverse effects such as drowsiness, sedation, dizziness, orthostatic hypotension, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.
Pindolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of pindolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving pindolol concomitantly.
Pioglitazone: (Moderate) Because risperidone has been associated with hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic states, diabetic coma, and overall worsening of glycemic control, patients taking antidiabetic agents such as thiazolidinediones should be closely monitored for worsening glycemic control when risperidone is instituted. Possible mechanisms for risperidone-related effects on glycemic control include insulin resistance or direct beta-cell inhibition.
Pirbuterol: (Minor) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de

pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Posaconazole: (Severe) The concurrent use of posaconazole and risperidone is contraindicated. Posaconazole has been associated with QT prolongation as well as rare cases of torsade de pointes (TdP) and risperidone has a possible risk of QT prolongation and TdP. In addition, posaconazole is a CYP3A4 inhibitor and use with other drugs that may prolong the QT interval and are metabolized through CYP3A4, such as risperidone, should be avoided.

Potassium-sparing diuretics: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Pramipexole: (Major) Pramipexole is a potent dopamine-receptor agonist. Dopamine-receptor antagonists, including antipsychotics may antagonize the effects of pramipexole. In general, the atypical antipsychotics are less likely to interfere with antiparkinson treatments than traditional antipsychotic agents. However, antipsychotics should be avoided during therapy for Parkinson's disease unless the benefit of the drug outweighs the risk of decreased therapeutic response to levodopa or other treatments.

Pramlintide: (Moderate) Patients taking pramlintide should be closely monitored for worsening glycemic control when atypical antipsychotics are instituted. Atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Prazosin: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.

Prilocaine; Epinephrine: (Major) The alpha-adrenergic effects of epinephrine can be blocked during concurrent administration of risperidone. This blockade can cause an apparently paradoxical condition called 'epinephrine reversal'. The vasoconstrictive properties of dopamine infusion can be decreased due to the alpha-adrenergic blocking capability of risperidone. The use of other agents for vascular support is recommended when needed.

Primaquine: (Major) Due to the potential for QT interval prolongation with primaquine, caution is advised with other drugs that prolong the QT interval. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with primaquine include risperidone.

Primidone: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.

Procainamide: (Major) Risperidone should be used cautiously and with close monitoring with procainamide. Procainamide administration is associated with QT prolongation and torsades de pointes (TdP). Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically.

Prochlorperazine: (Moderate) Prochlorperazine, a phenothiazine, is associated with a possible risk for QT prolongation. Prochlorperazine may increase the risk of QT prolongation if coadministered with drugs with a possible risk for QT prolongation, such as risperidone. Co-administration of prochlorperazine with atypical agents (e.g., lurasidone and others) may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.

Promethazine: (Major) Promethazine and risperidone have been associated with a possible risk for QT prolongation and torsade de pointes (TdP) and caution is advisable during coadministration. In addition, because promethazine is a phenothiazine derivative, concurrent use with antipsychotics may increase the risk of drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. Although the incidence of tardive dyskinesia from these combinations has not been established and data are very limited, the risk may be increased during combined use versus monotherapy.

Propafenone: (Major) Both risperidone and propafenone are associated with a risk for QT prolongation and torsade de pointes (TdP); therefore, caution is advised during concurrent use. If coadministration is required and the patient has risk factors for cardiac disease or arrhythmias, close monitoring is recommended.

Propoxyphene: (Moderate) Concomitant use of propoxyphene with other CNS depressants, such as risperidone, can potentiate the effects of propoxyphene on respiratory depression and/or sedation.

Propranolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of propranolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving propranolol concomitantly.
Protriptyline: (Moderate) Concurrent use of risperidone and tricyclic antidepressants should be approached with caution. Risperidone has a possible risk for QT prolongation and torsade de pointes and tricyclic antidepressants have rarely been associated with these effects, particularly when given in excessive doses or following overdose. No dosage adjustment of risperidone is recommended based on pharmacokinetic data; however, additive CNS effects are possible.
Quazepam: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.
Quetiapine: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include quetiapine. Quetiapine may be associated with a significant prolongation of the QTc interval in rare instances. Additionally, according to the manufacturer, no significant kinetic drug interactions were identified when quetiapine was coadministered with haloperidol or risperidone.
Quinidine: (Severe) Quinidine administration is associated with QT prolongation and torsades de pointes (TdP). Quinidine inhibits CYP2D6 and has QT-prolonging actions; quinidine is contraindicated with other drugs that prolong the QT interval and are metabolized by CYP2D6 as the effects on the QT interval may be increased during concurrent use of these agents. Drugs that prolong the QT and are substrates for CYP2D6 that are contraindicated with quinidine include risperidone.
Quinine: (Major) Concurrent use of quinine and risperidone should be avoided if possible due to an increased risk for QT prolongation and torsade de pointes (TdP). If coadministration is required and the patient has risk factors for cardiac disease or arrhythmias, close monitoring is recommended.
Ranitidine: (Moderate) Although dosage adjustments are not necessary, patients receiving concurrent treatment with risperidone and ranitidine should be monitored for risperidone-induced side effects or extrapyramidal symptoms. Pharmacokinetic data indicate that increased exposure to risperidone and its active metabolite occurs during use of ranitidine. This interaction is thought to be the result of inhibition of CYP3A4, one of the isoenzymes responsible for the metabolism of risperidone.
Ranolazine: (Major) Risperidone and ranolazine have a possible risk for QT prolongation and torsade de pointes (TdP); therefore, caution is recommended during concurrent use. If coadministration is required and the patient has risk factors for cardiac disease or arrhythmias, close monitoring is recommended.
Rasagiline: (Moderate) Atypical antipsychotics may reduce the beneficial effects of rasagiline by blocking dopamine. Additive CNS effects are possible; advise against engaging in tasks requiring mental alertness until the effects of the drug combination are known to the patient. Monoamine oxidase type B inhibitors increase the availability of central dopamine. Antipsychotics may induce pseudoparkinisonism (e.g., shuffling gait, tremor), thereby exacerbating Parkinson's disease symptoms. In addition, dopaminergic medications, including rasagiline, may cause a sudden onset of somnolence which sometimes has resulted in motor vehicle accidents. Patients may not perceive warning signs, such as excessive drowsiness, or they may report feeling alert immediately prior to the event. Atypical antipsychotics may exacerbate sedation or hypotension.
Regadenoson: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include regadenoson.
Remifentanil: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including remifentanil.
Repaglinide: (Moderate) Patients taking meglitinides should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.
Reserpine: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Ribociclib: (Major) Avoid coadministration of ribociclib with risperidone if possible due to an increased risk for QT prolongation and torsade de pointes (TdP). Ribociclib has been shown to prolong the QT interval in a concentration-dependent manner and risperidone has been associated with a possible risk for QT prolongation and/or TdP, primarily in the overdose setting. If coadministration is required and the patient has known risk factors for cardiac disease or arrhythmias, close monitoring is recommended.
Ribociclib; Letrozole: (Major) Avoid coadministration of ribociclib with risperidone if possible due to an increased risk for QT prolongation and torsade de pointes (TdP). Ribociclib has been shown to prolong the QT interval in a concentration-dependent manner and risperidone has been associated with a possible risk for QT prolongation and/or TdP, primarily in the overdose setting. If coadministration is required and the patient has known risk factors for cardiac disease or arrhythmias, close monitoring is recommended.

Rifampin: (Major) The manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer like rifampin. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials. Potent inducers of CYP3A4, such as rifampin, may decrease plasma concentrations of risperidone and its active metabolite. In an open, randomized two-phase crossover study, rifampin caused significant decreases in risperidone plasma concentrations in healthy volunteers.
Rilpivirine: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include rilpivirine. Supratherapeutic doses of rilpivirine (75 to 300 mg/day) have caused QT prolongation; caution is advised when administering rilpivirine with other drugs that may prolong the QT or PR interval.
Ritonavir: (Major) If coadministration of risperidone and ritonavir is required, careful monitoring for increased adverse effects of risperidone is recommended. Risperidone is metabolized by CYP3A4, CYP2D6, and P-gp and ritonavir is an inhibitor of CYP3A4, CYP2D6, and P-gp. In addition, both drugs have been associated with QT prolongation, and additive QT effects are possible. A decreased dosage of risperidone may be required.
Rolapitant: (Major) Coadministration of risperidone, a CYP2D6 substrate, and rolapitant, a CYP2D6 inhibitor, may increase plasma concentrations of risperidone. The inhibitory effect of rolapitant lasts for at least 7 days, and may last longer after single dose administration. When oral risperidone is given with a CYP2D6 inhibitor, the dose of risperidone should be reduced; do not exceed 8 mg/day PO in adults. When initiating therapy, titrate risperidone slowly. Upon discontinuation of the CYP2D6 inhibitor, the risperidone dose should be re-evaluated and increased if necessary. For the long-acting injection, the current adult dosage should be re-evaluated when a CYP2D6 inhibitor is initiated or discontinued. When initiation of a CYP2D6 inhibitor is considered, patients may be placed on a lower dose of injectable risperidone 2 to 4 weeks prior to initiation to adjust for the expected increase in risperidone plasma concentrations. For patients receiving a 25 mg dose, it is recommended to maintain the 25 mg dose upon initiation of the CYP2D6 inhibitor unless clinical judgment warrants lowering the dose to 12.5 mg or interrupting risperidone therapy. The efficacy of the 12.5 mg dose has not been evaluated in clinical trials. When injectable risperidone is initiated in patients already receiving a CYP2D6 inhibitor, a starting dose of 12.5 mg can be considered. The Cmax and AUC of another CYP2D6 substrate, dextromethorphan, were increased by 120% and 160%, respectively, on day 1 with rolapitant, and by 180% and 230%, respectively, on day 8 after rolapitant administration.
Romidepsin: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, appropriate cardiovascular monitoring precautions should be considered, such as the monitoring of electrolytes and ECGs at baseline and periodically during treatment. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include romidepsin.
Ropinirole: (Major) Ropinirole is a potent dopamine-receptor agonist. Dopamine-receptor antagonists, including antipsychotics may antagonize the effects of ropinirole. In general, the atypical antipsychotics are less likely to interfere with antiparkinson treatments than traditional antipsychotic agents. However, antipsychotics should be avoided during therapy for Parkinson's disease unless the benefit of the drug outweighs the risk of decreased therapeutic response to levodopa or other treatments.
Rosiglitazone: (Moderate) Because risperidone has been associated with hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic states, diabetic coma, and overall worsening of glycemic control, patients taking antidiabetic agents such as thiazolidinediones should be closely monitored for worsening glycemic control when risperidone is instituted. Possible mechanisms for risperidone-related effects on glycemic control include insulin resistance or direct beta-cell inhibition.
Rotigotine: (Moderate) Rotigotine is a dopamine-receptor agonist. Dopamine-receptor antagonists, including atypical antipsychotics should be avoided concurrently because they may antagonize the effects of rotigotine. In general, atypical antipsychotics are less likely to interfere with antiparkinson treatments than traditional antipsychotics. However, antipsychotics should be avoided during therapy for Parkinson's Disease unless the benefit of the drug outweighs the risk of decreased therapeutic response to rotigotine or other treatments.
Safinamide: (Moderate) Atypical antipsychotics may reduce the beneficial effects of safinamide by blocking dopamine. Additive CNS effects are possible; advise against engaging in tasks requiring mental alertness until the effects of the combination are known. Monoamine oxidase type B inhibitors increase the availability of central dopamine. Antipsychotics may induce pseudoparkinism (e.g., shuffling gait, tremor), thereby exacerbating Parkinson's disease symptoms. In addition, dopaminergic medications, including safinamide, may cause a sudden onset of somnolence which sometimes has resulted in motor vehicle accidents. Patients may not perceive warning signs, such as excessive drowsiness, or they may report feeling alert immediately prior to the event. Atypical antipsychotics may exacerbate sedation or hypotension.
Salmeterol: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account

the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Sapropterin: (Moderate) Caution is advised with the concomitant use of sapropterin and risperidone as coadministration may result in increased systemic exposure of risperidone. Risperidone is a substrate for the drug transporter P-glycoprotein (P-gp); in vitro data show that sapropterin may inhibit P-gp. If these drugs are used together, closely monitor for increased side effects of risperidone.

Saquinavir: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Saquinavir boosted with ritonavir increases the QT interval in a dose-dependent fashion, which may increase the risk for serious arrhythmias such as TdP. Avoid coadministration. If no acceptable alternative therapy is available, perform a baseline ECG prior to initiation of concomitant therapy and carefully follow monitoring recommendations.

Saxagliptin: (Moderate) Patients taking saxagliptin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Secobarbital: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.

Selegiline: (Moderate) Due to the potential for additive CNS and cardiovascular effects, MAOIs and antipsychotics should be used together cautiously; some experts recommend initiating low doses of the antipsychotic and careful dosage titration.

Sertraline: (Major) Because both sertraline and risperidone are associated with a possible risk of QT prolongation and torsade de pointes (TdP), the combination should be used cautiously. These medications are commonly used together in clinical practice; however, if the patient has risk factors for cardiac disease or arrhythmias, close monitoring is recommended.

Short-acting beta-agonists: (Minor) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Sibutramine: (Major) Caution and close monitoring should be observed when administering sibutramine with drugs that are dopamine antagonists such as the atypical antipsychotics. Monitor for CNS depression, changes in mood or behavior, and for other drug-related adverse reactions. Sibutramine has not been systematically evaluated in combination with antipsychotic medications. Sibutramine is a serotonin reuptake inhibitor that also inhibits norepinephrine and dopamine reuptake. Patients receiving these combinations should be monitored for the emergence of serotonin syndrome or neuroleptic malignant syndrome-like reactions.

Simvastatin; Sitagliptin: (Moderate) Patients taking sitagliptin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Sitagliptin: (Moderate) Patients taking sitagliptin should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Sodium picosulfate; Magnesium oxide; Anhydrous citric acid: (Moderate) Use caution when prescribing sodium picosulfate; magnesium oxide; anhydrous citric acid in patients taking concomitant medications that are known to induce Antidiuretic Hormone Secretion (SIADH), such as antipsychotics, as these drugs may increase the risk of water retention and/or electrolyte imbalance.

Sofosbuvir; Velpatasvir; Voxilaprevir: (Moderate) Plasma concentrations of risperidone, a P-glycoprotein (P-gp) substrate, may be increased when administered concurrently with voxilaprevir, a P-gp inhibitor. Monitor patients for increased side effects if these drugs are administered concurrently.

Solifenacin: (Major) Due to the potential for QT prolongation and torsade de pointes (TdP), caution is advised when administering solifenacin with risperidone. If coadministration is chosen, and the patient has known risk

factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Solifenacin has been associated with dose-dependent prolongation of the QT interval; TdP has been reported during post-marketing use, although causality was not determined. Risperidone has also been associated with a possible risk for QT prolongation and/or TdP; however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting.

Sorafenib: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, ECG monitoring is recommended; closely monitor the patient for QT interval prolongation. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include sorafenib.

Sotalol: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, such as sotalol, taking into account the patient's underlying disease state(s) and additional potential risk factors. Sotalol administration is associated with QT prolongation and torsades de pointes (TdP). Proarrhythmic events should be anticipated after initiation of therapy and after each upward dosage adjustment. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically.

Sufentanil: (Moderate) Concomitant use of sufentanil with other CNS depressant, such as risperidone, can potentiate sufentanil-induced CNS and cardiovascular effects and the duration of these effects. A dose reduction of one or both drugs may be warranted.

Sulfamethoxazole; Trimethoprim, SMX-TMP, Cotrimoxazole: (Major) QT prolongation resulting in ventricular tachycardia and torsade de pointes (TdP) have been reported during post-marketing use of sulfamethoxazole; trimethoprim. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously and with close monitoring with sulfamethoxazole; trimethoprim include risperidone.

Sulfonylureas: (Moderate) Patients taking sulfonylureas should be closely monitored for worsening glycemic control when an atypical antipsychotic is instituted. The atypical antipsychotics have been associated with metabolic changes, including hyperglycemia, diabetic ketoacidosis, hyperosmolar, hyperglycemic states, and diabetic coma. Possible mechanisms include atypical antipsychotic-induced insulin resistance or direct beta-cell inhibition. While a causal relationship has not been established, temporal associations of atypical antipsychotic therapy with the aggravation of diabetes mellitus have been reported.

Sunitinib: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include sunitinib.

Tacrolimus: (Major) Tacrolimus causes QT prolongation. Reducing the tacrolimus dose, close monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended when coadministrating tacrolimus with other substrates and/or inhibitors of CYP3A4 that also have the potential to prolong the QT interval such as risperidone.

Tamoxifen: (Major) Caution is advised with the concomitant use of tamoxifen and risperidone due to an increased risk of QT prolongation and torsade de pointes (TdP). If coadministration is necessary, monitor for evidence of QT prolongation if the patient has known risk factors for cardiac disease or arrhythmias. Tamoxifen has been reported to prolong the QT interval, usually in overdose or when used in high doses. Rare case reports of QT prolongation have also been described when tamoxifen is used at lower doses. Risperidone has been associated with a possible risk for QT prolongation and/or TdP. Reports of QT prolongation and TdP during risperidone therapy have been noted primarily in the overdosage setting.

Tapentadol: (Moderate) Additive CNS depressive effects are expected if tapentadol is used in conjunction with other CNS depressants. Severe hypotension, profound sedation, coma, or respiratory depression may occur. Prior to concurrent use of tapentadol in patients taking a CNS depressant, assess the level of tolerance to CNS depression that has developed, the duration of use, and the patient's overall response to treatment. Consider the patient's use of alcohol or illicit drugs. If a CNS depressant is used concurrently with tapentadol, a reduced dosage of tapentadol and/or the CNS depressant is recommended. If the extended-release tapentadol tablets are used concurrently with a CNS depressant, it is recommended to use an initial tapentadol dose of 50 mg PO every 12 hours. Monitor patients for sedation and respiratory depression.

Telaprevir: (Moderate) Close clinical monitoring is advised when administering risperidone with telaprevir due to an increased potential for risperidone-related adverse events. If risperidone dose adjustments are made, re-adjust the dose upon completion of telaprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of risperidone. Risperidone is a substrate of the drug efflux transporter P-glycoprotein (PGP) and of the hepatic isoenzyme CYP3A4; telaprevir is an inhibitor of both the efflux protein and the isoenzyme. Coadministration may result in elevated risperidone plasma concentrations.

Telavancin: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s)

and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include telavancin.
Telithromycin: (Major) Both risperidone and telithromycin have a risk for QT prolongation and torsade de pointes (TdP); therefore, caution is advisable during concurrent use. If coadministration is required and the patient has risk factors for cardiac disease or arrhythmias, close monitoring is recommended.
Telotristat Ethyl: (Moderate) Use caution if coadministration of telotristat ethyl and risperidone is necessary, as the systemic exposure of risperidone may be decreased resulting in reduced efficacy. If these drugs are used together, monitor patients for suboptimal efficacy of risperidone; consider increasing the dose of risperidone if necessary. Risperidone is a CYP3A4 substrate. The mean Cmax and AUC of another sensitive CYP3A4 substrate was decreased by 25% and 48%, respectively, when coadministered with telotristat ethyl; the mechanism of this interaction appears to be that telotristat ethyl increases the glucuronidation of the CYP3A4 substrate.
Temazepam: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.
Terazosin: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Terbutaline: (Minor) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.
Tetrabenazine: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Tetrabenazine causes a small increase in the corrected QT interval (QTc). The manufacturer recommends avoiding concurrent use of tetrabenazine with other drugs known to prolong QTc such as risperidone. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. In addition, the risk of adverse effects such as drowsiness, sedation, dizziness, orthostatic hypotension, neuroleptic malignant syndrome, or extrapyramidal symptoms may be increased.
Thiazide diuretics: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Thiazolidinediones: (Moderate) Because risperidone has been associated with hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic states, diabetic coma, and overall worsening of glycemic control, patients taking antidiabetic agents such as thiazolidinediones should be closely monitored for worsening glycemic control when risperidone is instituted. Possible mechanisms for risperidone-related effects on glycemic control include insulin resistance or direct beta-cell inhibition.
Thiopental: (Major) Potent inducers of CYP3A4, such as barbiturates, may decrease plasma concentrations of risperidone and its active metabolite. Therefore, the manufacturer of oral risperidone recommends a slow upward titration of the risperidone dose as needed up to double the patient's usual dose during use of a 3A4 inducer. When using Risperdal Consta, the patient will require close monitoring for 4 to 8 weeks when starting an inducer. A lower dose of Risperdal Consta may be prescribed between 2 to 4 weeks before the planned discontinuation of the inducer to adjust for the expected increase in plasma concentrations of risperidone and its active metabolite. For patients treated with the recommended dose of Risperdal Consta 25 mg and discontinuing the inducer, it is recommended to continue the 25 mg dose unless a reduction to 12.5 mg or discontinuation of treatment is indicated. The efficacy of the 12.5 mg dose has not been studied in clinical trials.
Thioridazine: (Severe) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer primarily in the overdosage setting. However, due to the risk of additive QT prolongation and potential for serious arrhythmias, the concurrent use of risperidone and thioridazine is considered contraindicated.
Thiothixene: (Major) Co-administration of risperidone with thiothixene may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.
Timolol: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of timolol. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving timolol concomitantly.
Tiotropium; Olodaterol: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.

Tipranavir: (Major) Coadministration of risperidone, a CYP2D6 substrate, and tipranavir, a potent CYP2D6 inhibitor, may increase plasma concentrations of risperidone. When oral risperidone is given with a potent CYP2D6 inhibitor, re-evaluate the risperidone dosing and do not exceed risperidone 8 mg/day PO in adults. When initiating therapy, titrate risperidone slowly. Upon discontinuation of the CYP2D6 inhibitor, the risperidone dose should be re-evaluated and increased if necessary. For the long-acting risperidone injection, the current adult dosage should be closely monitored when a potent CYP2D6 inhibitor is initiated or discontinued. An adjustment of the dose may be required.
Tizanidine: (Major) Risperidone should be used cautiously and with close monitoring with tizanidine. Tizanidine administration may result in QT prolongation. Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically.
Tolcapone: (Major) Atypical antipsychotics are central dopamine antagonists and may inhibit the clinical response to antiparkinsonian agents with dopamine agonist properties by blocking dopamine receptors in the brain. Due to the CNS depressant effects of atypical antipsychotics, additive drowsiness may occur with Parkinson's treatments like entacapone or tolcapone. In general, atypical antipsychotics are less likely to interfere with these therapies than traditional antipsychotic agents.
Tolterodine: (Major) Because both tolterodine and risperidone have the potential for QT prolongation and torsade de pointes (TdP), caution is advised during concurrent use. If coadministration is required and the patient has risk factors for cardiac disease or arrhythmias, close monitoring is recommended.
Toremifene: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with risperidone include toremifene. Toremifene has been shown to prolong the QTc interval in a dose- and concentration-related manner.
Torsemide: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Tramadol: (Major) Concurrent use of tramadol and risperidone should be avoided if possible due to a possible increased risk of seizures. Seizures have been reported in patients receiving monotherapy with tramadol or antipsychotics at recommended doses. In addition, due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally-acting medications such as tramadol.
Trandolapril; Verapamil: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Tranylcypromine: (Moderate) Due to the potential for additive CNS and cardiovascular effects, MAOIs and antipsychotics should be used together cautiously; some experts recommend initiating low doses of the antipsychotic and careful dosage titration.
Trazodone: (Major) Avoid coadministration of trazodone and risperidone. Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Trazodone can prolong the QT/QTc interval at therapeutic doses. In addition, there are post-marketing reports of TdP. Therefore, the manufacturer recommends avoiding trazodone in patients receiving other drugs that increase the QT interval.
Treprostinil: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Triazolam: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including anxiolytics, sedatives, and hypnotics.
Tricyclic antidepressants: (Moderate) Concurrent use of risperidone and tricyclic antidepressants should be approached with caution. Risperidone has a possible risk for QT prolongation and torsade de pointes and tricyclic antidepressants have rarely been associated with these effects, particularly when given in excessive doses or following overdose. No dosage adjustment of risperidone is recommended based on pharmacokinetic data; however, additive CNS effects are possible.
Trifluoperazine: (Moderate) Trifluoperazine, a phenothiazine, is associated with a possible risk for QT prolongation. Theoretically, trifluoperazine may increase the risk of QT prolongation if coadministered with drugs with a possible risk for QT prolongation, such as risperidone. Co-administration of trifluoperazine with atypical agents (e.g., lurasidone and others) may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The likelihood of these pharmacodynamic interactions varies based upon the individual properties of the co-administered antipsychotic agent. Although the incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited, the risk appears to be increased during use of a conventional and atypical antipsychotic versus use of a conventional antipsychotic alone.
Trimipramine: (Moderate) Concurrent use of risperidone and tricyclic antidepressants should be approached with caution. Risperidone has a possible risk for QT prolongation and torsade de pointes and tricyclic

antidepressants have rarely been associated with these effects, particularly when given in excessive doses or following overdose. No dosage adjustment of risperidone is recommended based on pharmacokinetic data; however, additive CNS effects are possible.
Triprolidine: (Moderate) Due to the primary CNS effects of risperidone, caution should be used when risperidone is given in combination with other centrally acting medications including sedating H1-blockers. Additive drowsiness or other CNS effects may occur.
Triptorelin: (Major) Androgen deprivation therapy (e.g., triptorelin) prolongs the QT interval; the risk may be increased with the concurrent use of drugs that may prolong the QT interval such as risperidone. Additionally, antipsychotics such as risperidone may induce hyperprolactinemia, resulting in down-regulation of the number of pituitary GnRH receptors and having the potential to interfere with the response to triptorelin therapy.
Ulipristal: (Minor) In vitro data indicate that ulipristal may be an inhibitor of P-glycoprotein (P-gp) at clinically relevant concentrations. Thus, co-administration of ulipristal and P-gp substrates such as risperidone may increase risperidone concentrations. With single doses of ulipristal for emergency contraception it is not clear this interaction will have clinical consequence. In the absence of clinical data, co-administration of ulipristal (when given daily) and P-gp substrates is not recommended.
Umeclidinium; Vilanterol: (Moderate) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes(TdP); however, data are currently lacking to establish causality in association with TdP. Reports of QT prolongation and TdP are noted by the manufacturer, primarily in the overdosage setting. Risperidone should be used cautiously with other agents that might prolong the QT interval, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored. Drugs with a possible risk for QT prolongation that should be used cautiously and with close monitoring with risperidone include the beta-agonists. Beta-agonists may be associated with adverse cardiovascular effects including QT interval prolongation, usually at higher doses and/or when associated with hypokalemia.
Valproic Acid, Divalproex Sodium: (Minor) Coadministration of risperidone and valproate may result in a minor increase in peak plasma concentrations of valproic acid; however, dosage adjustments of valproic acid are not recommended. In one evaluation, concomitant administration of risperidone 4 mg/day and valproate 1,000 mg/day resulted in a 20% increase in valproate peak plasma concentration (Cmax) and there was no effect on the pre-dose or average plasma concentrations and exposure (AUC) of valproate. The mechanism of this interaction is not known.
Vandetanib: (Major) The manufacturer of vandetanib recommends avoiding coadministration with other drugs that prolong the QT interval due to an increased risk of QT prolongation and torsade de pointes (TdP). Vandetanib can prolong the QT interval in a concentration-dependent manner. TdP and sudden death have been reported in patients receiving vandetanib. Risperidone has been associated with a possible risk for QT prolongation and/or TdP. Reports of QT prolongation and TdP during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. If coadministration is necessary, an ECG is needed, as well as more frequent monitoring of the QT interval. If QTcF is greater than 500 msec, interrupt vandetanib dosing until the QTcF is less than 450 msec; then, vandetanib may be resumed at a reduced dose. It is possible that vandetanib can increase concentrations of risperidone as well. Risperidone is a substrate of, and has a strong affinity for, P-glycoprotein (P-gp). Coadministration with vandetanib increased the Cmax and AUC of another P-gp substrate by 29% and 23%, respectively.
Vardenafil: (Major) Because both risperidone and vardenafil have been associated with a possible risk for QT prolongation and torsade de pointes (TdP), cautious use is recommended. Patients with known risk factors for cardiac disease or arrhythmias should be closely monitored. Therapeutic (10 mg) and supratherapeutic (80 mg) doses of vardenafil produce an increase in QTc interval (e.g., 4 to 6 msec calculated by individual QT correction). Reports of QT prolongation and TdP during risperidone therapy have occurred primarily in the setting of overdose.
Vasodilators: (Moderate) Risperidone may induce orthostatic hypotension and thus enhance the hypotensive effects of antihypertensive agents. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Vemurafenib: (Major) Vemurafenib and risperidone have been associated with a possible risk for QT prolongation and/or torsade de pointes (TdP). Additionally, coadministration of risperidone, a CYP2D6 substrate, with CYP2D6 inhibitors may increase plasma concentrations of risperidone; however, a clinically significant kinetic interaction with vemurafenib is unlikely because vemurafenib is only a mild inhibitor of CYP2D6.
Venlafaxine: (Major) Because both venlafaxine and risperidone are associated with a possible risk of QT prolongation, caution is advisable during coadministration.
Verapamil: (Moderate) Risperidone has been associated with orthostatic hypotension and may enhance the hypotensive effects of antihypertensive agents. Clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive medications. Lower initial doses or slower dose titration of risperidone may be necessary in patients receiving antihypertensive agents concomitantly.
Voriconazole: (Major) Caution is advised when administering voriconazole with risperidone due to the potential for additive effects on the QT interval and increased exposure to risperidone. Both drugs are associated with QT prolongation; coadministration may increase this risk. Voriconazole has also been associated with rare cases of torsades de pointes, cardiac arrest, and sudden death. In addition, coadministration of voriconazole (a CYP3A4 inhibitor) with risperidone (a CYP3A4 substrate) may result in elevated risperidone plasma concentrations and an increased risk for adverse events, including QT prolongation. If these drugs are given together, closely monitor for prolongation of the QT interval. Rigorous attempts to correct any electrolyte abnormalities (i.e., potassium, magnesium, calcium) should be made before initiating concurrent therapy.
Vorinostat: (Major) Risperidone has been associated with a possible risk for QT prolongation and/or torsade de pointes; however, data are currently lacking to establish causality in association with torsades de pointes (TdP). Reports of QT prolongation and torsades de pointes during risperidone therapy are noted by the manufacturer, primarily in the overdosage setting. Since risperidone may prolong the QT interval, it should be used cautiously with other agents also known to have this effect, such as vorinostat, taking into account the patient's underlying disease state(s) and additional potential risk factors. If coadministration is chosen, and the patient has known risk factors for cardiac disease or arrhythmia, then the patient should be closely monitored clinically.

Zaleplon: (Moderate) Additive CNS-depressant effects may occur with the atypical antipsychotics and zaleplon. In addition, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of CNS depressants than with zaleplon alone. In premarketing studies, zaleplon potentiated the CNS effects of a phenothiazine antipsychotic for at least 2 to 4 hours. Other antipsychotics may also have additive CNS effects with zaleplon.
Ziconotide: (Moderate) Risperidone is a CNS depressant medication that may increase drowsiness, dizziness, and confusion that are associated with ziconotide.
Ziprasidone: (Major) The benefits and risks of combining antipsychotics should be considered prior to treatment initiation. Both ziprasidone and risperidone have been associated with a possible risk for QT prolongation and torsade de pointes. In addition, coadministration of antipsychotics may increase the risk of adverse effects such as drowsiness, dizziness, orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, or seizures. The incidence of tardive dyskinesia from combination antipsychotic therapy has not been established and data are very limited.
Zolpidem: (Moderate) Additive CNS-depressant effects may occur with the atypical antipsychotics and zolpidem. In addition, sleep-related behaviors, such as sleep-driving, are more likely to occur during concurrent use of zolpidem and other CNS depressants than with zolpidem alone.
Zonisamide: (Moderate) Zonisamide may cause decreased sweating (oligohidrosis), elevated body temperature (hyperthermia), heat intolerance, or heat stroke. The manufacturer recommends caution in using concurrent drug therapies that may predispose patients to heat-related disorders such as antipsychotics. Monitor patients for heat intolerance, decreased sweating, or increased body temperature if zonisamide is used with any of these agents.

PREGNANCY AND LACTATION

Pregnancy

According to the manufacturer of oral risperidone, a decision should be made whether to discontinue breast-feeding or to discontinue the drug taking into account the importance of the drug to the mother. Risperidone and 9-hydroxyrisperidone are present in human breast milk and there is a potential for serious adverse reactions in the nursing infant. The manufacturer of the depot risperidone injection (Risperdal Consta) states that breast-feeding should not occur for at least 12 weeks after the last injection. Antipsychotics may cause elevated prolactin levels and galactorrhea to varying degrees, and thus may interfere with proper lactation. Four case reports document the excretion of risperidone and 9-hydroxyrisperidone into breast milk; the milk/plasma ratio for all 4 women was less than 0.5 for both compounds. The calculated relative doses each infant received were 2.3, 2.8, 4.3 and 4.7% of the maternal doses (weight adjusted). When the infant plasma samples were assayed, risperidone and 9-hydroxyrisperidone were not detectable. Each infant was thriving and no reported adverse effects were attributable to risperidone. According to the authors, maternal use of risperidone is unlikely to be a significant risk for the breast-fed infant in the short-term, but long-term risks are unknown and the potential risks/benefits should be evaluated. Due to individual variability in response to antipsychotics, it may be prudent to continue the existing regimen if ongoing treatment is deemed necessary during breast-feeding. However, if an alternative antipsychotic is needed, other atypical agents such as olanzapine or quetiapine may be considered. Data related to the safety of antipsychotics during breast-feeding are limited and chronic administration of any antipsychotic during breast-feeding should be avoided if possible. Regardless of the antipsychotic used, the nursing infant should be closely monitored for excessive drowsiness, lethargy, and developmental delays. Combination treatment with antipsychotics may increase the risk of these adverse events. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

MECHANISM OF ACTION

Although the exact mechanism of action of antipsychotics is unknown, it has been proposed that central blockade of dopamine D-2 in the mesolimbic pathway targets the positive symptoms of schizophrenia (e.g., hallucinations, delusions). Optimal blockade is within the range of 65% to 75% of D-2 receptors, leading to effectiveness while preserving safety. The receptor binding profile of many conventional antipsychotics (e.g., haloperidol, fluphenazine) involves a preferred affinity for D-2 receptors over serotonin receptors, whereas the receptor binding profile of some atypical antipsychotics (such as risperidone) involves a high affinity for 5-HT2A receptor blockade. It has been theorized that antagonism of serotonin in the prefrontal cortex leads to an increase in dopamine release thereby creating the potential for improvement in the negative symptoms (e.g., blunted affect, social withdrawal) and cognitive deficits observed in schizophrenia. It should be noted that modulation of serotonin receptors alone does not have an antipsychotic effect. Antipsychotic drugs appear to have neuroplastic effects, including synaptic plasticity (remodeling of synapses and development of new neuron connections) and neurogenesis (new neuron development), which may partially explain the delay in some of the therapeutic effects of antipsychotics.

Dopamine blockade by antipsychotics in the nigrostriatal pathway of the brain is thought to cause extrapyramidal symptoms (EPS) such as pseudoparkinsonism, dystonic reactions, and akathisia. It has been suggested that blockade of 5-HT2A receptors leads to increased output of dopaminergic neurons into the striatum, decreasing the likelihood of extrapyramidal reactions. Dopamine receptor blockade in the tuberoinfundibular tract results in prolactin release, with the potential for hyperprolactinemia and its adverse clinical effects. The likelihood of developing hyperprolactinemia is generally related to the potency of the individual antipsychotic to block D-2 receptors. Thus, based on its D-2 receptor binding profile, risperidone has a higher propensity for causing prolactin elevations than most other atypical antipsychotics.

Risperidone exhibits strong antagonist activity at alpha-1 receptors, which likely contributes to adverse cardiovascular effects such as orthostatic hypotension, which may be associated with dizziness, syncope, and

reflex tachycardia. The alpha-1 blocking effect is also thought to be responsible for priapism, a potentially severe adverse reaction which has occurred during post-marketing use of the drug. High affinity at H-1 histamine receptors has also been demonstrated, which partially accounts for adverse effects such as sedation and weight gain. Risperidone has low to moderate affinity for serotonin 5-HT1A, 5-HT1C, and 5-HT1D receptors and a weak affinity for dopamine D-1 receptors and haloperidol-sensitive sigma binding sites. There is no affinity for cholinergic or beta-adrenergic receptors.

PHARMACOKINETICS

Risperidone is administered orally or as a long-acting depot intramuscular injection. Both risperidone and its metabolites are highly protein bound and are preferentially distributed to the frontal cortex and striatum in the brain, where tissue half-lives are longer than in the plasma. Risperidone and its metabolite are excreted in human breast milk. Animal studies show that risperidone crosses the placenta to some extent. Risperidone is metabolized by CYP2D6 and also via N-dealkylation. Risperidone and the principal, active metabolite, 9-hydroxyrisperidone, are equally effective. Oral risperidone has a half-life of about 3 hours in extensive metabolizers and 20 hours in poor metabolizers; the half-life of 9-hydroxyrisperidone is about 21 hours in extensive metabolizers and 30 hours in poor metabolizers. Excretion of metabolites is mainly renal, with a small amount excreted in the feces; about 70% of an oral dose is eliminated in the urine. The apparent half-life of risperidone plus 9-hydroxyrisperidone after IM depot injection administration is 3 to 6 days and is related to the erosion of the microspheres and subsequent absorption of risperidone. No accumulation of risperidone was observed during up to 12 months of use in patients treated every 2 weeks with 25 mg or 50 mg risperidone depot injection. The elimination phase is complete approximately 7 to 8 weeks after the last injection.

Affected cytochrome P450 isoenzymes and drug transporters: CYP2D6, CYP3A4, P-glycoprotein (P-gp)
Risperidone is metabolized to an active metabolite, 9-hydroxyrisperidone, which has equal activity to risperidone. Risperidone is a primary substrate of CYP2D6. Drugs that are inhibitors or inducers of CYP2D6 could lead to elevated or lowered serum concentrations of the parent drug risperidone, respectively. Serum concentrations of 9-hydroxy-risperidone could decline resulting in reduced efficacy if a CYP2D6 inhibitor is initiated. Risperidone is also a substrate of CYP3A4, but to a lesser degree than CYP2D6. The manufacturer recommends a dosage adjustment of risperidone during co-administration of carbamazepine, a CYP3A4 and P-gp inducer. Other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) may also cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. In vitro studies demonstrated that drugs metabolized by 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism. Risperidone is a weak inhibitor of CYP2D6 in vitro; therefore, the drug is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. Risperidone has a strong affinity for P-gp.

Oral Route

Risperidone is administered orally as tablets, orally disintegrating tablets, or as an oral solution. Dosages of the orally disintegrating tablets and oral solution are bioequivalent to comparable dosages of the original-formulation tablets. Absorption is complete; these dosage forms of risperidone can be administered without regard to meals. Peak plasma concentrations are achieved within 1 to 2 hours. Plasma concentrations are dose-proportional for risperidone and its active metabolite.

Intramuscular Route

Intramuscular (IM) Depot Route (Risperdal Consta)
Intramuscular risperidone is injected into the gluteal or deltoid muscle. These routes of administration are considered bioequivalent and interchangeable. After a single IM (gluteal) injection of risperidone, the main release of the drug starts from 3 weeks onward, is maintained from 4 to 6 weeks, and subsides by 7 weeks after the IM injection. Therefore, oral antipsychotic supplementation should be given during the first 3 weeks of treatment with risperidone to maintain therapeutic concentrations until the main release of risperidone has begun. The combination of the release profile and the dosage regimen (IM injections every 2 weeks) of risperidone results in sustained therapeutic concentrations. Steady-state plasma concentrations are reached after 4 injections and are maintained for 4 to 6 weeks after the last injection. Plasma concentrations of risperidone, 9-hydroxyrisperidone (the major metabolite), and risperidone plus 9-hydroxyrisperidone are linear over the dosing range of 25 mg to 50 mg.

Back to top