RISPERIDONE

**Brands**
- Risperdal
- CONSTA

*see index for additional brand names*

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: dopamine, serotonin, norepinephrine receptor antagonist (DSN-RAn)
- Atypical antipsychotic (serotonin-dopamine antagonist; second generation antipsychotic; also a mood stabilizer)

**Commonly Prescribed for**
*(bold for FDA approved)*
- Schizophrenia, ages 13 and older (oral, long-acting microspheres intramuscularly)
- Delaying relapse in schizophrenia (oral)
- Other psychotic disorders (oral)
- Acute mania/mixed mania, ages 10 and older (oral, monotherapy and adjunct to lithium or valproate)
- Autism-related irritability in children ages 5–16
- Bipolar maintenance (long-acting microspheres intramuscularly, monotherapy and adjunct to lithium or valproate)
- Bipolar depression
- Behavioral disturbances in dementias
- Behavioral disturbances in children and adolescents
- Disorders associated with problems with impulse control

**How the Drug Works**
- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
- Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms
- Interactions at a myriad of other neurotransmitter receptors may contribute to risperidone's efficacy

*Specifically, 5HT7 antagonist properties may contribute to antidepressant actions*

**How Long Until It Works**
- Psychotic and manic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition and affective stabilization
- Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients require up to 16–20 weeks to show a good response, especially on cognitive symptoms

**If It Works**
- Most often reduces positive symptoms in schizophrenia but does not eliminate them
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
- Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenic patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
- Such patients are considered super-responders or “awakeners” since they may be well enough to be employed, live independently, and sustain long-term relationships
- Many bipolar patients may experience a reduction of symptoms by half or more
- Continue treatment until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis
- For second and subsequent episodes of psychosis, treatment may need to be indefinite
- Even for first episodes of psychosis, it may be preferable to continue treatment indefinitely to avoid subsequent episodes
- Treatment may not only reduce mania but also prevent recurrences of mania in bipolar disorder

**If It Doesn’t Work**
- Try one of the other atypical antipsychotics (olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, amisulpride, asenapine, ioperidone, lurasidone)
- If 2 or more antipsychotic monotherapies do not work, consider clozapine
Some patients may require treatment with a conventional antipsychotic
If no first-line atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection
Consider initiating rehabilitation and psychotherapy such as cognitive remediation
Consider presence of concomitant drug abuse

Best Augmenting Combos for Partial Response or Treatment Resistance
- Valproic acid (valproate, divalproex, divalproex ER)
- Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
- Lithium
- Benzodiazepines

Tests
Before starting an atypical antipsychotic
- Weigh all patients and track BMI during treatment
- Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
- Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
- Determine if the patient is
  - overweight (BMI 25.0–29.9)
  - obese (BMI ≥30)
  - has pre-diabetes (fasting plasma glucose 100–125 mg/dL)
  - has diabetes (fasting plasma glucose >126 mg/dL)
  - has hypertension (BP >140/90 mm Hg)
  - has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
- Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting an atypical antipsychotic
- BMI monthly for 3 months, then quarterly

Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained >5% of initial weight
- Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic
- Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness, and clouding of sensorium, even coma
- Should check blood pressure in the elderly before starting and for the first few weeks of treatment
- Monitoring elevated prolactin levels of dubious clinical benefit
- Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and risperidone should be discontinued at the first sign of decline of WBC in the absence of other causative factors

SIDE EFFECTS
How Drug Causes Side Effects
- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects, especially at high doses
- By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin
- Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown
**DOSING AND USE**

### Usual Dosage Range
- 2–8 mg/day orally for acute psychosis and bipolar disorder
- 0.5–2.0 mg/day orally for children and elderly
- 12.5–50 mg depot intramuscularly every 2 weeks (see Risperidone Microspheres section after Pearls for dosing and use)

### Dosage Forms
- Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 6 mg
- Orally disintegrating tablets 0.5 mg, 1 mg, 2 mg
- Liquid 1 mg/mL – 30 mL bottle
- Risperidone long-acting depot microspheres formulation for deep intramuscular administration: 12.5 mg vial/kit, 25 mg vial/kit, 37.5 mg vial/kit, 50 mg vial/kit

### How to Dose
- In adults with psychosis in nonemergency settings, initial dosage recommendation is 1 mg/day orally in 2 divided doses
- Increase each day by 1 mg/day orally until desired efficacy is reached
- Maximum generally 16 mg/day orally
- Typically maximum effect is seen at 4–8 mg/day orally
- See also the Switching section, after Pearls
- Can be administered on a once daily schedule as well as twice daily orally

### Notable Side Effects
- May increase risk for diabetes and dyslipidemia
- Dose-dependent extrapyramidal symptoms
- Dose-related hyperprolactinemia
- Dose-dependent dizziness, insomnia, anxiety, sedation
  - Nausea, constipation, abdominal pain, weight gain
  - Tachycardia, dose-dependent sexual dysfunction
  - Rare tardive dyskinesia (much reduced risk compared to conventional antipsychotics)
  - Rare orthostatic hypotension, usually during initial dose titration

### Life-Threatening or Dangerous Side Effects
- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics)
- Rare seizures

### Weight Gain
- Many patients experience and/or can be significant in amount
- Can become a health problem in some
- May be less than for some antipsychotics, more than for others

### Sedation
- Many patients experience and/or can be significant in amount
- Usually transient
- May be less than for some antipsychotics, more than for others

### What to Do About Side Effects
- Wait
- Wait
- Wait
Dosing Tips – Oral Formulation

- **Less may be more:** lowering the dose in some patients with stable efficacy but side effects may reduce side effects without loss of efficacy, especially for doses over 6 mg/day orally
- **Target doses for best efficacy/best tolerability in many adults with psychosis or bipolar disorder may be 2–6 mg/day (average 4.5 mg/day) orally**
  - Low doses may not be adequate in difficult patients
  - Rather than raise the dose above these levels in acutely agitated patients requiring acute antipsychotic actions, consider augmentation with a benzodiazepine or conventional antipsychotic, either orally or intramuscularly
  - Rather than raise the dose above these levels in partial responders, consider augmentation with a mood-stabilizing anticonvulsant, such as valproate or lamotrigine
  - Approved for use up to 16 mg/day orally, but data suggest that risk of extrapyramidal symptoms is increased above 6 mg/day
  - Risperidone oral solution is not compatible with cola or tea
  - Children and elderly may need to have oral twice daily dosing during initiation and titration of drug dosing and then can switch to oral once daily when maintenance dose is reached
  - Children and elderly should generally be dosed at the lower end of the dosage spectrum
  - Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose

- Rarely lethal in monotherapy overdose; sedation, rapid heartbeat, convulsions, low blood pressure, difficulty breathing

Long-Term Use

- Approved to delay relapse in long-term treatment of schizophrenia
- Often used for long-term maintenance in bipolar disorder and various behavioral disorders

Habit Forming

- No

How to Stop

- See Switching section of individual agents for how to stop risperidone
- Rapid oral discontinuation may lead to rebound psychosis and worsening of symptoms

Pharmacokinetics

- Metabolites are active
- Metabolized by CYP450 2D6
- Parent drug of oral formulation has 20–24 hour half-life
- Long-acting risperidone has 3–6 day half-life
- Long-acting risperidone has elimination phase of approximately 7–8 weeks after last injection
- Food does not affect absorption

Drug Interactions

- May increase effect of antihypertensive agents
- May antagonize levodopa, dopamine agonists
- Clearance of risperidone may be reduced and thus plasma levels increased by clozapine; dosing adjustment usually not necessary
- Coadministration with carbamazepine may decrease plasma levels of risperidone
- Coadministration with fluoxetine and paroxetine may increase plasma levels of risperidone
- Since risperidone is metabolized by CYP450 2D6, any agent that inhibits this enzyme could theoretically raise risperidone plasma levels; however, dose reduction of risperidone is usually not necessary when such combinations are used

Other Warnings/Precautions

- Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
- Risperidone should be used cautiously in patients at risk for aspiration pneumonia, as dysphagia has been reported
- Priapism has been reported

Do Not Use

- If there is a proven allergy to risperidone or paliperidone
SPECIAL POPULATIONS

Renal Impairment
- Initial 0.5 mg orally twice a day for first week; increase to 1 mg twice a day during second week; dosage increases above 1.5 mg twice a day should occur at least 1 week apart
- LAI risperidone should not be administered unless patient has demonstrated tolerability of at least 2 mg/day orally
- LAI risperidone should be dosed at 25 mg every 2 weeks; oral administration should be continued for 3 weeks after the first injection

Hepatic Impairment
- Initial 0.5 mg orally twice a day for first week; increase to 1 mg twice a day during second week
- LAI risperidone should not be administered unless patient has demonstrated tolerability of at least 2 mg/day orally
- LAI risperidone should be dosed at 25 mg every 2 weeks; oral administration should be continued for 3 weeks after the first injection

Cardiac Impairment
- Drug should be used with caution because of risk of orthostatic hypotension
- When administered to elderly patients with atrial fibrillation, may increase the chances of stroke

Elderly
- Initial 0.5 mg orally twice a day; increase by 0.5 mg twice a day; titrate once a week for doses above 1.5 mg twice a day
- Recommended dose of long-acting risperidone is 25 mg every 2 weeks; oral administration should be continued for 3 weeks after the first injection
- Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events

Children and Adolescents
- Approved for use in schizophrenia (ages 13 and older), mania/mixed episodes (ages 10 and older), and irritability associated with autism (ages 5–16)
- Risperidone is the most frequently used atypical antipsychotic in children and adolescents
- Clinical experience and early data suggest risperidone is safe and effective for behavioral disturbances in children and adolescents
- Children and adolescents using risperidone may need to be monitored more often than adults

Pregnancy
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLL or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
- Early findings of infants exposed to risperidone in utero do not show adverse consequences
- Risperidone may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy
- Effects of hyperprolactinemia on the fetus are unknown
- National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388 or http://
RISPERIDONE (continued)

**Breast Feeding**
- Some drug is found in mother’s breast milk
- Recommended either to discontinue drug or bottle feed
- Infants of women who choose to breast feed while on risperidone should be monitored for possible adverse effects

**THE ART OF PSYCHOPHARMACOLOGY**

**Potential Advantages**
- Some cases of psychosis and bipolar disorder refractory to treatment with other antipsychotics
- Often a preferred treatment for dementia with aggressive features
- Often a preferred atypical antipsychotic for children with behavioral disturbances of multiple causations
- Noncompliant patients (LAI risperidone)
- Long-term outcomes may be enhanced when compliance is enhanced (LAI risperidone)

**Potential Disadvantages**
- Patients for whom elevated prolactin may not be desired (e.g., possibly pregnant patients; pubescent girls with amenorrhea; postmenopausal women with low estrogen who do not take estrogen replacement therapy)

**Primary Target Symptoms**
- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Cognitive functioning
- Unstable mood (both depression and mania)
- Aggressive symptoms

**Pearls**
- Well accepted for treatment of behavioral symptoms in children and adolescents, but may have more sedation and weight gain in pediatric populations than in adult populations
- Well accepted for treatment of agitation and aggression in elderly demented patients
- Many anecdotal reports of utility in treatment-refractory cases and for positive symptoms of psychosis in disorders other than schizophrenia
- Hyperprolactinemia in women with low estrogen may accelerate osteoporosis
- Less weight gain than some antipsychotics, more than others
- Less sedation than some antipsychotics, more than others
- Increased risk of stroke may be most relevant in the elderly with atrial fibrillation
- May cause more motor side effects than some other atypical antipsychotics, especially when administered to patients with Parkinson’s disease or Lewy body dementia
- Patients with inadequate responses to atypical antipsychotics may benefit from determination of plasma drug levels and, if low, a dosage increase even beyond the usual prescribing limits
- Patients with inadequate responses to atypical antipsychotics may also benefit from a trial of augmentation with a conventional antipsychotic or switching to a conventional antipsychotic
- However, long-term polypharmacy with a combination of a conventional antipsychotic with an atypical antipsychotic may combine their side effects without clearly augmenting the efficacy of either
- For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy with 2 atypical antipsychotics or with 1 atypical antipsychotic and 1 conventional antipsychotic may be useful or even necessary while closely monitoring
- In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic
- Although a frequent practice by some prescribers, adding 2 conventional antipsychotics together has little rationale and may reduce tolerability without clearly enhancing efficacy
### Microspheres

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<tr>
<td>Injection volume</td>
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- The long half-lives of depot antipsychotics mean that one must either adequately load the dose (if possible) or provide oral supplementation.
- The failure to adequately load the dose leads either to prolonged cross-titration from oral antipsychotic or to sub-therapeutic antipsychotic plasma levels for weeks or months in patients who are not receiving (or adhering to) oral supplementation.
- Because plasma antipsychotic levels increase gradually over time, dose requirements may ultimately decrease from initial; obtaining periodic plasma levels can be beneficial to prevent unnecessary plasma level creep.
- The time to get a blood level for patients receiving LAI is the morning of the day they will receive their next injection.
- Advantages: also indicated for bipolar I maintenance (adjunct); pharmacokinetics are linear and stable over time.
- Disadvantages: Tmax is long (21 days) and loading is not possible, thus necessitating oral coverage for 3–4 weeks; split doses are not possible since drug is not in a solution (i.e., half a syringe is not necessarily half the drug dose); vials require refrigeration storage.
- Response threshold is generally 20 ng/mL; the tolerability threshold is poorly defined.
- Changes in blood levels due to dosage changes (or missed dose) are not apparent for 3–4 weeks, so titration should occur at intervals of no less than 4 weeks.
- Two different dosage strengths of LAI risperidone should not be combined in a single administration.
- Missed dose: if dose is 2 or more weeks late, oral coverage for 3 weeks while reinitiating injections may be necessary.
- Steady-state plasma concentrations are maintained for 4–6 weeks after the last injection.

### Usual Dosage Range
- 12.5–50 mg/2 weeks

### How to Dose
- Not recommended for patients who have not first demonstrated tolerability to oral risperidone (in clinical trials, 2 oral or short-acting IM doses are generally used to establish tolerability).
- Conversion from oral: oral coverage is required for 3–4 weeks; 2 mg oral risperidone is approximately 25 mg LAI every 2 weeks.

### Dosing Tips
- With LAIs, the absorption rate constant is slower than the elimination rate constant, thus resulting in “flip-flop” kinetics; i.e., time to steady-state is a function of absorption rate, while concentration at steady-state is a function of elimination rate.
- The rate-limiting step for plasma drug levels for LAIs is not drug metabolism, but rather slow absorption from the injection site.
- In general, 5 half-lives of any medication are needed to achieve 97% of steady-state levels.
- Two different dosage strengths of LAI risperidone should not be combined in a single administration.
- Missed dose: if dose is 2 or more weeks late, oral coverage for 3 weeks while reinitiating injections may be necessary.
- Steady-state plasma concentrations are maintained for 4-6 weeks after the last injection.
Discontinuation of oral antipsychotic can begin following a 3–4 week oral coverage period

How to discontinue oral formulations

- Down-titration is not required for: amisulpride, aripiprazole, brexpiprazole, cariprazine, paliperidone ER
- 1-week down-titration is required for: iloperidone, lurasidone, risperidone, ziprasidone
- 3–4-week down-titration is required for: asenapine, olanzapine, quetiapine
- 4+-week down-titration is required for: clozapine
- For patients taking benzodiazepine or anticholinergic medication, this can be continued during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis. Once the patient is stable on LAI, these can be tapered one at a time as appropriate.
**Switching from Oral Antipsychotics to Risperidone**

- With aripiprazole, amisulpride, and paliperidone ER, immediate stop is possible; begin risperidone at an intermediate dose.
- Concomitant use with paliperidone ER is not recommended; paliperidone ER is the active metabolite of risperidone, and the combination of the 2 may lead to additive active antipsychotic fraction exposure.
- Clinical experience has shown that quetiapine, olanzapine, and asenapine should be tapered off slowly over a period of 3–4 weeks, to allow patients to readapt to the withdrawal of blocking cholinergic, histaminergic, and alpha 1 receptors.
- Clozapine should always be tapered off slowly, over a period of 4 weeks or more.

* Benzodiazepine or anticholinergic medication can be administered during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis.

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Suggested Reading


