ZIPRASIDONE

**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
- IM formulation can reduce agitation in 15 minutes

**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 (risperidone, olanzapine, quetiapine, aripiprazole, paliperidone, amisulpride, asenapine, iloperidone, lurasidone)
- If 2 or more antipsychotic monotherapies do not work, consider clozapine

---

**Therapeutics**

**Brands**
- Geodon
*see index for additional brand names*

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: dopamine and serotonin receptor antagonist (DS_RAn)
- Atypical antipsychotic (serotonin-dopamine antagonist; second-generation antipsychotic; also a mood stabilizer)

**Commonly Prescribed for**
*(bold for FDA approved)*
- Schizophrenia
- Delaying relapse in schizophrenia
- Acute agitation in schizophrenia (intramuscular)
- Acute mania/mixed mania
- Bipolar maintenance
- Other psychotic disorders
- 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 ziprasidone’s efficacy
  - Specifically, interactions at 5HT2C and 5HT1A receptors may contribute to efficacy for cognitive and affective symptoms in some patients
  - Specifically, interactions at 5HT1D and 5HT7 receptors and at serotonin and norepinephrine transporters (especially at high doses) may contribute to efficacy for affective symptoms in some patients
• 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
• Routine EKGs for screening or monitoring of dubious clinical value
• EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or those taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfl oxacin, etc.)
• Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements
• 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 ziprasidone 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, especially at high doses
By blocking dopamine 2 receptors in the striatum, it can cause motor side effects (unusual)

Mechanism of any possible weight gain is unknown; weight gain is not common with ziprasidone and may thus have a different mechanism from atypical antipsychotics for which weight gain is common or problematic

Mechanism of any possible increased incidence of diabetes or dyslipidemia is unknown; early experience suggests these complications are not clearly associated with ziprasidone and if present may therefore have a different mechanism from that of atypical antipsychotics associated with an increased incidence of diabetes and dyslipidemia

Notable Side Effects

Activation (at very low to low doses)
- Dizziness, extrapyramidal symptoms, sedation (dose-dependent), dystonia at high doses
- Nausea, dry mouth (dose-dependent)
- Asthenia, skin rash
- Orthostatic hypotenison (dose-dependent)

Life-Threatening or Dangerous Side Effects

- Rare but serious skin condition known as Drug Reaction with Eosinophilia (DRESS)
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics)
- Rare tardive dyskinesia (much reduced risk compared to conventional antipsychotics)
- Rare seizures
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis

Weight Gain

- Reported in a few patients, especially those with low BMIs, but not expected
- Less frequent and less severe than for most other antipsychotics

Sedation

- Some patients experience, especially at high doses

May be less than for some antipsychotics, more than for others
- Usually transient and at higher doses
- Can be activating at low doses

What to Do About Side Effects

- Wait

- Usually dosed twice daily, so take more of the total daily dose at bedtime to help reduce daytime sedation
- Anticholinergics may reduce motor side effects when present
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia

For activating side effects at low doses, raise the dose

For sedating side effects at high doses, lower the dose

Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects

- Benztropine or trihexyphenidyl for motor side effects
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- Schizophrenia: 40–200 mg/day (in divided doses) orally
- Bipolar disorder: 80–160 mg/day (in divided doses) orally
- 10–20 mg intramuscularly

Dosage Forms

- Capsules 20 mg, 40 mg, 60 mg, 80 mg
- Injection 20 mg/mL

How to Dose

- Schizophrenia (according to manufacturer): initial oral dose 20 mg twice a day; however, 40 mg twice a day or 60 mg twice a day may be better tolerated in many patients (less activation); maximum approved dose 100 mg twice a day
- Bipolar disorder (according to manufacturer): initial oral dose 40 mg twice a day; on day 2 increase to 60 or 80 mg twice a day
• For intramuscular formulation, recommended dose is 10–20 mg given as required; doses of 10 mg may be administered every 2 hours; doses of 20 mg may be administered every 4 hours; maximum daily dose 40 mg intramuscularly; should not be administered for more than 3 consecutive days
• See also The Art of Switching section, after Pearls

### Dosing Tips

• More may be much more: clinical practice suggests ziprasidone often under-dosed, then switched prior to adequate trials, perhaps due to unjustified fears of QTc prolongation
• Dosing many patients at 20–40 mg twice a day is too low and in fact activating, perhaps due to potent 5HT2C antagonist properties
• Paradoxically, such activation is often reduced by increasing the dose to 60–80 mg twice a day, perhaps due to increasing amounts of dopamine 2 receptor antagonism
• Best efficacy in schizophrenia and bipolar disorder is at doses >120 mg/day, but only a minority of patients are adequately dosed in clinical practice
• Recommended to be taken with food because food can double bioavailability by increasing absorption and thus increasing plasma drug levels
• Meals of a few hundred calories (e.g., turkey sandwich and a piece of fruit) or more are necessary to enhance the absorption of ziprasidone
• Some patients respond better to doses >160 mg/day and up to 320 mg/day in 2 divided doses (i.e., 80–160 mg twice a day)
• Many patients do well with a single daily oral dose, usually at bedtime
• QTc prolongation at 320 mg/day not significantly greater than at 160 mg/day
• 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
• Children and elderly should generally be dosed at the lower end of the dosage spectrum
• Ziprasidone intramuscular can be given short-term, both to initiate dosing with oral ziprasidone or another oral antipsychotic and to treat breakthrough agitation in patients maintained on oral antipsychotics
• QTc prolongation of intramuscular ziprasidone is the same or less than with intramuscular haloperidol
• Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

### Overdose
• Rarely lethal in monotherapy overdose; sedation, slurred speech, transitory hypertension

### 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 ziprasidone
• Rapid oral discontinuation may lead to rebound psychosis and worsening of symptoms

### Pharmacokinetics
• Mean half-life 6.6 hours
• Protein binding >99%
• Metabolized by CYP450 3A4
• Absorption is approximately doubled if taken with food

### Drug Interactions
• Neither CYP450 3A4 nor CYP450 2D6 inhibitors significantly affect ziprasidone plasma levels
• Little potential to affect metabolism of drugs cleared by CYP450 enzymes
• May enhance the effects of antihypertensive drugs
No dose adjustment necessary

Cardiac Impairment
• Ziprasidone is contraindicated in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure
• Should be used with caution in other cases of cardiac impairment because of risk of orthostatic hypotension

Elderly
• Some patients may tolerate lower doses better
• 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
• Not officially recommended for patients under age 18
• Clinical experience and early data suggest ziprasidone may be safe and effective for behavioral disturbances in children and adolescents
• Children and adolescents using ziprasidone may need to be monitored more often than adults and may tolerate lower doses better

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 (PLLR 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
• Ziprasidone may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy
• National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388 or http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/

Breast Feeding
• Unknown if ziprasidone is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
  ✺ Recommended either to discontinue drug or bottle feed
• Infants of women who choose to breast feed while on ziprasidone should be monitored for possible adverse effects

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

Pearls
• Recent landmark head-to-head study in schizophrenia suggests lower metabolic side effects and comparable efficacy compared to some other atypical and conventional antipsychotics
  ✺ When given to patients with obesity and dyslipidemia associated with prior treatment with another atypical antipsychotic, many experience weight loss and decrease in fasting triglycerides
• QTc prolongation fears are often exaggerated and not justified since QTc prolongation with ziprasidone is not dose-related and few drugs have any potential to increase ziprasidone’s plasma levels
• Efficacy may be underestimated since ziprasidone is mostly under-dosed (<120 mg/day) in clinical practice
  ✺ Well accepted in clinical practice when wanting to avoid weight gain because less weight gain than most other atypical antipsychotics
• May not have diabetes or dyslipidemia risk, but monitoring is still indicated
• Less sedation than some antipsychotics, more than others (at moderate to high doses)
• More activating than some other antipsychotics at low doses
• Anecdotal reports of utility in treatment-resistant cases, especially when adequately dosed
• A short-acting intramuscular dosage formulation is available
• Approved for mania in children ages 10–17
• 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
• 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

THE ART OF SWITCHING

Switching from Oral Antipsychotics to Ziprasidone

• With aripiprazole, amisulpride, and paliperidone ER, immediate stop is possible; begin ziprasidone at an intermediate dose
• 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

<table>
<thead>
<tr>
<th>-target dose</th>
<th>dose</th>
<th>ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>iloperidone</td>
</tr>
<tr>
<td>lurasidone</td>
</tr>
<tr>
<td>risperidone</td>
</tr>
<tr>
<td>ziprasidone</td>
</tr>
<tr>
<td>1 week</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>asenapine</td>
</tr>
<tr>
<td>olanzapine</td>
</tr>
<tr>
<td>quetiapine</td>
</tr>
<tr>
<td>ziprasidone</td>
</tr>
<tr>
<td>1 week</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>clozapine</td>
</tr>
<tr>
<td>ziprasidone</td>
</tr>
<tr>
<td>1 week</td>
</tr>
<tr>
<td>1 week</td>
</tr>
<tr>
<td>1 week</td>
</tr>
<tr>
<td>1 week</td>
</tr>
<tr>
<td>1 week</td>
</tr>
</tbody>
</table>
Suggested Reading


