ASENAPINE

**Therapeutics**

**Brands**  • SAPHRIS

*see index for additional brand names*

**Generic?**  No

**Class**

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

**Commonly Prescribed for**

*(bold for FDA approved)*

• Schizophrenia, acute and maintenance (adults)
• Acute mania/mixed mania, monotherapy (ages 10 to 17 and in adults)
• Acute mania/mixed mania, adjunct to lithium or valproate (adults)
• Other psychotic disorders
• Bipolar maintenance
• Bipolar depression
• Treatment-resistant depression
• Behavioral disturbances in dementia
• 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

*Serotonin 2C, serotonin 7, and alpha 2 antagonist properties may contribute to antidepressant actions*

**How Long Until It Works**

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

**If It Works**

• Most often reduces positive symptoms but does not eliminate them
• Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
• Most schizophrenia patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
• Perhaps 5–15% of schizophrenia 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
• 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, ziprasidone, aripiprazole, paliperidone, iloperidone, amisulpride, 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid (valproate, divalproex, divalproex ER)</td>
<td>For seizure control and mood stabilization</td>
</tr>
<tr>
<td>Other mood-stabilizing anticonvulsants</td>
<td>Carbamazepine, oxcarbazepine, lamotrigine</td>
</tr>
<tr>
<td>Lithium</td>
<td>For mood stabilization</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>For anxiety and agitation control</td>
</tr>
</tbody>
</table>

## 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)
  - Pre-diabetes (fasting plasma glucose 100–125 mg/dL)
  - Diabetes (fasting plasma glucose >126 mg/dL)
  - Hypertension (BP >140/90 mm Hg)
  - 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

## 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
- By blocking dopamine 2 receptors in the pituitary, it can theoretically cause elevations in prolactin
- Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown

### Notable Side Effects

- Sedation, dizziness
- Oral hypoesthesia
- Application site reactions: oral ulcers, blisters, peeling/sloughing, inflammation
- Extrapyramidal symptoms, akathisia
- May increase risk for diabetes and dyslipidemia
- Rare tardive dyskinesia (much reduced risk compared to conventional antipsychotics)
- Orthostatic hypotension

### Life-Threatening or Dangerous Side Effects

- Type 1 hypersensitivity reactions (anaphylaxis, angioedema, low blood pressure, rapid heart rate, swollen tongue, difficulty breathing, wheezing, rash)
**ASENAPINE**

**How to Dose**
- Must be administered sublingually; patients may not eat or drink for 10 minutes following administration
- **Schizophrenia**: initial 10 mg/day in 2 divided doses; maximum dose generally 20 mg/day in 2 divided doses; limited experience with once daily administration
- **Bipolar mania (adults, monotherapy)**: initial 20 mg/day in 2 divided doses; can reduce dose to 10 mg/day in 2 divided doses if there are adverse effects
- **Bipolar mania (adults, adjunct)**: initial 10 mg/day in 2 divided doses; can increase to 20 mg/day in 2 divided doses
- **Bipolar mania (children, monotherapy)**: initial 5 mg/day in 2 divided doses; after 3 days can increase to 10 mg/day in 2 divided doses; after 3 more days can increase to 20 mg/day in 2 divided doses
- Pediatric patients may be more sensitive to dystonia with initial dosing if the recommended titration schedule is not followed

**Dosing Tips**
- Asenapine is not absorbed after swallowing (less than 2% bioavailable orally) and thus must be administered sublingually (35% bioavailable), as swallowing would render asenapine inactive
- Patients should be instructed to place the tablet under the tongue and allow it to dissolve completely, which will occur in seconds; tablet should not be divided, crushed, chewed, or swallowed
- Patients may not eat or drink for 10 minutes following sublingual administration so that the drug in the oral cavity can be absorbed locally and not washed into the stomach (where it would not be absorbed)
- Once daily use seems theoretically possible because the half-life of asenapine is 13–39 hours, but this has not been extensively studied and may be limited by the need to expose the limited sublingual surface area to a limited amount of sublingual drug dosage
- Some patients may respond to doses greater than 20 mg/day but no single administration should be greater than 10 mg, thus necessitating 3 or 4 separate daily doses

**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**
- Occurs in a significant minority
- May be less than for some antipsychotics, more than for others

**Sedation**
- Many experience and/or can be significant in amount

**What to Do About Side Effects**
- Wait
- Wait
- Wait
- Anticholinergics may reduce motor side effects when present
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
- 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

**Usual Dosage Range**
- 10–20 mg/day in 2 divided doses for schizophrenia
- 10–20 mg/day in 2 divided doses for bipolar mania

**Dosage Forms**
- Sublingual tablet 2.5 mg, 5 mg, 10 mg
ASENAPINE (continued)

- Due to rapid onset of action, can be used as a rapid acting “prn” or “as needed” dose for agitation or transient worsening of psychosis or mania instead of an injection
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose
- Agitation, confusion

Long-Term Use
- Not studied, but long-term maintenance treatment is often necessary for schizophrenia and bipolar disorder

Habit Forming
- No

How to Stop
- Down-titration, over 2–4 weeks when possible, especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- Rapid discontinuation could theoretically lead to rebound psychosis and worsening of symptoms

Pharmacokinetics
- Half-life 13–39 hours
- Inhibits CYP450 2D6
- Substrate for CYP450 1A2
- Optimal bioavailability is with sublingual administration (~35%); if food or liquid is consumed within 10 minutes of administration bioavailability decreases to 28%; bioavailability decreases to 2% if swallowed

Drug Interactions
- May increase effects of antihypertensive agents
- May antagonize levodopa, dopamine agonists
- CYP450 1A2 inhibitors (e.g., fluvoxamine) can raise asenapine levels
- Via CYP450 2D6 inhibition, asenapine could theoretically interfere with the analgesic effects of codeine, and increase the plasma levels of some beta blockers and of atomoxetine
- Via CYP450 2D6 inhibition, asenapine could theoretically increase concentrations of thioridazine and cause dangerous cardiac arrhythmias

Other Warnings/Precautions
- Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
- Dysphagia has been associated with antipsychotic use, and asenapine should be used cautiously in patients at risk for aspiration pneumonia

Do Not Use
- If there is a proven allergy to asenapine

SPECIAL POPULATIONS

Renal Impairment
- Dose adjustment not generally necessary

Hepatic Impairment
- No dose adjustment necessary for mild to moderate impairment
- Not recommended for patients with severe hepatic impairment

Cardiac Impairment
- Drug should be used with caution 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
- Approved to treat acute manic/mixed episodes of bipolar I disorder in children ages 10 and older
- Children and adolescents using asenapine may need to be monitored more often than adults
Potential Advantages

- Patients requiring rapid onset of antipsychotic action without dosage titration

Potential Disadvantages

- Patients who are less likely to be adherent

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Cognitive symptoms
- Unstable mood (both depression and mania)
- Aggressive symptoms

Pearls

- Asenapine’s chemical structure is related to the antidepressant mirtazapine and it shares many of the same pharmacologic binding properties of mirtazapine plus many others
- Not approved for depression, but binding properties suggest potential use in treatment-resistant and bipolar depression
- Sublingual administration may require prescribing asenapine to reliable, adherent patients, or those who have someone who can supervise drug administration
- 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

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
- In animal studies, asenapine increased post-implantation loss and decreased pup weight and survival at doses similar to or less than recommended clinical doses; there was no increase in the incidence of structural abnormalities
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
- Asenapine may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy

Breast Feeding

- Unknown if asenapine 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 asenapine should be monitored for possible adverse effects

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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

THE ART OF SWITCHING

Switching from Oral Antipsychotics to Asenapine
• With aripiprazole, amisulpride, and paliperidone ER, immediate stop is possible; begin asenapine at middle dose
• With risperidone, ziprasidone, iloperidone, and luasidone: begin asenapine gradually, titrating over at least 2 weeks to allow patients to become tolerant to the sedating effect
* May need to taper clozapine slowly over 4 weeks or longer

Suggested Reading
