**THERAPEUTICS**

**Brands**
- Zyprexa
- Symbyax (olanzapine-fluoxetine combination)
- Relprevv

*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 (ages 13 and older)
- Maintaining response in schizophrenia
- Acute agitation associated with schizophrenia (intramuscular)
- Acute mania/mixed mania (monotherapy and adjunct to lithium or valproate) (ages 13 and older)
- Bipolar maintenance
- Acute agitation associated with bipolar I mania (intramuscular)
- Bipolar depression (in combination with fluoxetine [Symbyax])
- Treatment-resistant depression (in combination with fluoxetine [Symbyax])
- Other psychotic disorders
- Behavioral disturbances in dementias
- Behavioral disturbances in children and adolescents
- Disorders associated with problems with impulse control
- Borderline personality disorder

**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 olanzapine’s efficacy

  ✴ Specifically, antagonist actions at 5HT2C receptors may contribute to efficacy for cognitive and affective symptoms in some patients

  ✴ 5HT2C antagonist actions plus serotonin reuptake blockade of fluoxetine add to the actions of olanzapine when given as Symbyax (olanzapine-fluoxetine combination)

**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 15–30 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, quetiapine, ziprasidone, aripiprazole, paliperidone, amisulpride, asenapine, iloperidone, 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 comorbid drug abuse

Best Augmenting Combs for Partial Response or Treatment Resistance
Valproic acid (valproate, divalproex, divalproex ER)
Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
Lithium
Benzodiazepines
Fluoxetine and other antidepressants may be effective augmenting agents to olanzapine for bipolar depression, psychotic depression, and for unipolar depression not responsive to antidepressants alone (e.g., olanzapine-fluoxetine combination)

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

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
Patients with liver disease should have blood tests a few times a year
Patients with low white blood cell count (WBC) or history of drug-induced leukopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and olanzapine should be discontinued at the first sign of decline of WBC in the absence of other causative factors
OLANZAPINE

How Drug Causes Side Effects

- By blocking histamine 1 receptors in the brain, it can cause sedation and possibly weight gain
- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- By blocking muscarinic 1 receptors, it can cause dry mouth, constipation, and sedation
- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects (unusual)
- Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown but insulin regulation may be impaired by blocking pancreatic M3 muscarinic receptors

Notable Side Effects

* Probably increases risk for diabetes mellitus and dyslipidemia
- Dizziness, sedation
- Dry mouth, constipation, dyspepsia, weight gain
- Peripheral edema
- Joint pain, back pain, chest pain, extremity pain, abnormal gait, ecchymosis
- Tachycardia
- Orthostatic hypotension, usually during initial dose titration
- Rare tardive dyskinesia (much reduced risk compared to conventional antipsychotics)
- Rare rash on exposure to sunlight

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
- Rare but serious skin condition known as Drug Reaction with Eosinophilia (DRESS)
- Rare neuroleptic malignant syndrome (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

- Frequent and can be significant in amount
- Can become a health problem in some
- More than for some other antipsychotics, but never say always as not a problem in everyone

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
- Take at bedtime to help reduce daytime sedation
- Anticholinergics may reduce motor side effects such as akathisia when present, but rarely necessary
- 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

SIDE EFFECTS

DOSING AND USE

Usual Dosage Range

- 10–20 mg/day (oral or intramuscular)
- 6–12 mg olanzapine/25–50 mg fluoxetine (olanzapine-fluoxetine combination)
- 150–300 mg/2 weeks or 300–405 mg/4 weeks (see Olanzapine Pamoate after Pearls for dosing and use)

Dosage Forms

- Tablets 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg
- Orally disintegrating tablets 5 mg, 10 mg, 15 mg, 20 mg
• Intramuscular formulation 5 mg/mL, each vial contains 10 mg (available in some countries)
• Depot 210 mg, 300 mg, 405 mg
• Olanzapine-fluoxetine combination capsule (mg equivalent olanzapine/mg equivalent fluoxetine) 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, 12 mg/50 mg

How to Dose
• Initial 5–10 mg once daily orally; increase by 5 mg/day once a week until desired efficacy is reached; maximum approved dose is 20 mg/day
• For intramuscular formulation, recommended initial dose 10 mg; second injection of 5–10 mg may be administered 2 hours after first injection; maximum daily dose of olanzapine is 20 mg, with no more than 3 injections per 24 hours
• For olanzapine-fluoxetine combination, recommended initial dose 6 mg/25 mg once daily in evening; increase dose based on efficacy and tolerability; maximum generally 18 mg/75 mg

How to Stop
• See Switching section of individual agents for how to stop olanzapine
• 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
• Clearance of olanzapine is slightly reduced in women compared to men, so women may need lower doses than men
• Children and elderly should generally be dosed at the lower end of the dosage spectrum
• Olanzapine intramuscularly can be given short-term, both to initiate dosing with oral olanzapine or another oral antipsychotic and to treat breakthrough agitation in patients maintained on oral antipsychotics
• Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

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

Long-Term Use
• Approved to maintain response in long-term treatment of schizophrenia
• Approved for long-term maintenance in bipolar disorder
• Often used for long-term maintenance in various behavioral disorders

Habit Forming
• No

Pharmacokinetics
• Metabolites are inactive
• Parent drug has 21–54 hour half-life
• Substrate for CYP450 1A2 and 2D6
• Food does not affect absorption

Drug Interactions
• May increase effect of antihypertensive agents
• May antagonize levodopa, dopamine agonists
• Dose may need to be lowered if given with CYP450 1A2 inhibitors (e.g., fluvoxamine); raised if given in conjunction with CYP450 1A2 inducers (e.g., cigarette smoke, carbamazepine)
Other Warnings/Precautions

- Olanzapine is associated with a rare but serious skin condition known as Drug Reaction with Eosinophilia (DRESS). DRESS may begin as a rash but can progress to other parts of the body and can include symptoms such as fever, swollen lymph nodes, swollen face, inflammation of organs, and an increase in white blood cells known as eosinophilia. In some cases, DRESS can lead to death. Clinicians prescribing olanzapine should inform patients about the risk of DRESS; patients who develop a fever with rash and swollen lymph nodes or swollen face should seek medical care. Patients are not advised to stop their medication without consulting their prescribing clinician.

- Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)

- Use with caution in patients with prostatic hypertrophy, angle-closure glaucoma, paralytic ileus

- Patients receiving the intramuscular formulation of olanzapine should be observed closely for hypotension

- Intramuscular formulation is not generally recommended to be administered with parenteral benzodiazepines; if patient requires a parenteral benzodiazepine it should be given at least 1 hour after intramuscular olanzapine

- Olanzapine should be used cautiously in patients at risk for aspiration pneumonia, as dysphagia has been reported

Do Not Use

- If there is a known risk of angle-closure glaucoma (intramuscular formulation)

- If patient has unstable medical condition (e.g., acute myocardial infarction, unstable angina pectoris, severe hypotension and/or bradycardia, sick sinus syndrome, recent heart surgery) (intramuscular formulation)

- If there is a proven allergy to olanzapine

SPECIAL POPULATIONS

Renal Impairment

- No dose adjustment required for oral formulation

- Not removed by hemodialysis

- For intramuscular formulation, consider lower starting dose (5 mg)

Hepatic Impairment

- May need to lower dose

- Patients with liver disease should have liver function tests a few times a year

- For moderate to severe hepatic impairment, starting oral dose 5 mg; increase with caution

- For intramuscular formulation, consider lower starting dose (5 mg)

Cardiac Impairment

- Drug should be used with caution because of risk of orthostatic hypotension

Elderly

- Some patients may tolerate lower doses better

- Increased incidence of stroke

- For intramuscular formulation, recommended starting dose is 2.5–5 mg; a second injection of 2.5–5 mg may be administered 2 hours after first injection; no more than 3 injections should be administered within 24 hours

- 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 and manic/mixed episodes (ages 13 and older for both)

- Clinical experience and early data suggest olanzapine is probably safe and effective for behavioral disturbances in children and adolescents

531
• Children and adolescents using olanzapine may need to be monitored more often than adults
• Intramuscular formulation has not been studied in patients under 18 and is not recommended for use in this population

**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
• Early findings of infants exposed to olanzapine in utero currently do not show adverse consequences
• Olanzapine 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 olanzapine 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 olanzapine 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 augmenting agent in bipolar depression or treatment-resistant unipolar depression
* Patients needing rapid onset of antipsychotic action without drug titration
* Patients switching from intramuscular olanzapine to an oral preparation

**Potential Disadvantages**

* Patients concerned about gaining weight
* Patients with diabetes mellitus, obesity, and/or dyslipidemia

**Primary Target Symptoms**

* Positive symptoms of psychosis
* Negative symptoms of psychosis
* Cognitive symptoms
* Unstable mood (both depressed mood and mania)
* Aggressive symptoms

**Pearls**

• Recent landmark head-to-head study in schizophrenia suggests greater effectiveness (i.e., lower dropouts of all causes) at moderately high doses compared to some other atypical and conventional antipsychotics at moderate doses
• Same recent head-to-head study in schizophrenia suggests greater efficacy but greater metabolic side effects compared to some other atypical and conventional antipsychotics
• Well accepted for use in schizophrenia and bipolar disorder, including difficult cases
• Documented utility in treatment-refractory cases, especially at higher doses
• Documented efficacy as augmenting agent to SSRIs (fluoxetine) in nonpsychotic treatment-resistant major depressive disorder
• Documented efficacy in bipolar depression, especially in combination with fluoxetine
• More weight gain than many other antipsychotics – does not mean every patient gains weight
• Motor side effects unusual at low- to mid-doses
• Less sedation than for some other antipsychotics, more than for others
Controversial as to whether olanzapine has more risk of diabetes and dyslipidemia than other antipsychotics

- Cigarette smoke can decrease olanzapine levels and patients may require a dose increase if they begin or increase smoking

A short-acting intramuscular dosage formulation is available

- Long-acting intramuscular dosage formulation is also approved

- 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

### Usual Dosage Range

- 150–300 mg/2 weeks or 300–405 mg/4 weeks

### How to Dose

- Conversion from oral: dose should be loaded during the initial 8 weeks based on the prior stable oral dose of olanzapine

<table>
<thead>
<tr>
<th>Daily oral olanzapine dose</th>
<th>LAI dose: first 8 weeks</th>
<th>LAI dose: after 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>210 mg/2 weeks OR 405 mg/4 weeks</td>
<td>150 mg/2 weeks OR 300 mg/4 weeks</td>
</tr>
<tr>
<td>15 mg</td>
<td>300 mg/2 weeks OR 405 mg/4 weeks</td>
<td>210 mg/2 weeks OR 405 mg/4 weeks</td>
</tr>
<tr>
<td>20 mg</td>
<td>300 mg/2 weeks</td>
<td>300 mg/2 weeks</td>
</tr>
</tbody>
</table>

- Oral supplementation may be needed if adequate loading is not used

- Maximum dose 300 mg/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

- 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

### PamOate

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax</td>
<td>3–4 days</td>
</tr>
<tr>
<td>T1/2 with multiple dosing</td>
<td>30 days</td>
</tr>
<tr>
<td>Time to reach steady state</td>
<td>3 months</td>
</tr>
<tr>
<td>Able to be loaded</td>
<td>Yes</td>
</tr>
<tr>
<td>Dosing schedule (maintenance)</td>
<td>2 weeks or 4 weeks</td>
</tr>
<tr>
<td>Injection site</td>
<td>Intramuscular gluteal</td>
</tr>
</tbody>
</table>
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: efficacy advantage of oral olanzapine
- Disadvantages: 3-hour post-injection monitoring required due to risk (0.2%) of post-injection delirium from vascular breach
- Response threshold is generally 21 ng/mL; plasma levels greater than 176 ng/mL are generally not well tolerated

**SWITCHING FROM ORAL ANTIPSYCHOTICS TO OLANZAPINE PAMOATE**

**Expected Olanzapine Levels Without Oral Coverage**

- **Initiation at:**
  - 300 mg/2 weeks
  - 405 mg/4 weeks
  - 210 mg/2 weeks
  - 150 mg/2 weeks

- **Switch to:**
  - 300 mg/4 weeks

- **Loading period:**
  - Time (weeks): 0, 4, 8, 12

- **Maintenance period:**
  - Time (weeks): 0, 4, 8, 12, 16, 20, 24

- Average olanzapine plasma concentration at each injection (ng/ml)

- Discontinuation of oral antipsychotic can begin immediately if adequate loading is pursued
- How to discontinue oral formulations
  - Down-titration is not required for: amisulpride, aripiprazole, brexpiprazole, cariprazine, olanzapine, paliperidone ER
  - 1-week down-titration is required for: iloperidone, lurasidone, risperidone, ziprasidone, asenapine, quetiapine
  - 4+-week down-titration may be required for: clozapine

**Advantages:**
- Efficacy advantage of oral olanzapine

**Disadvantages:**
- 3-hour post-injection monitoring required due to risk (0.2%) of post-injection delirium from vascular breach
- Response threshold is generally 21 ng/mL; plasma levels greater than 176 ng/mL are generally not well tolerated
Switching from Oral Antipsychotics to Oral Olanzapine

- With aripiprazole, amisulpride, and paliperidone ER, immediate stop is possible; begin olanzapine at middle dose
- With risperidone, ziprasidone, iloperidone, and lurasidone, begin olanzapine 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

Citrome L. Adjunctive aripiprazole, olanzapine, or quetiapine for major depressive disorder: an analysis of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Postgrad Med 2010;122(4):39–48.