SECOND-GENERATION ANTIPSYCHOTIC

Olanzapine

Zyprexa, Zyprexa Zydis, Zyprexa IntraMuscular, Zyprexa Relprevv, Symbyax

Among the most effective antipsychotics available, and the most metabolically damaging; efficacy and weight gain travel together.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
10-20 mg/day PO	21-54 h (mean 30 h)	CYP1A2, UGT1A4	1-2 wks; 4-6 wks full

⚠ FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis; olanzapine is not approved for that use. When given with fluoxetine, the Symbyax boxed warning also applies. Zyprexa Relprevv carries a separate boxed warning for post-injection delirium and sedation syndrome.

INDICATIONS

- Schizophrenia in adults and adolescents ages 13-17, including maintenance treatment, with a long-acting injectable available for adults.
- Acute manic or mixed episodes of bipolar I disorder in adults and adolescents ages 13-17, as monotherapy or as adjunct to lithium or valproate.
- Maintenance monotherapy for bipolar I disorder in adults, where relapse prevention data are among the strongest in the class.
- Combined with fluoxetine for bipolar I depression in patients age 10 and older and for treatment-resistant depression in adults.
- Intramuscular olanzapine is approved for acute agitation in schizophrenia and bipolar I mania, and is used off-label for chemotherapy-induced nausea.

DOSING & TITRATION

- Schizophrenia in adults: start **5-10 mg/day PO** once daily, target **10 mg/day** after about one week, with a labeled maximum of **20 mg/day**.
- Bipolar mania: start **10-15 mg/day** as monotherapy or 10 mg/day when combined with lithium or valproate, adjusting by 5 mg no faster than daily.
- Adolescents start at **2.5-5 mg/day** with a 10 mg/day target, since they gain weight faster and more than adults at any given dose.
- Intramuscular olanzapine for agitation is **10 mg**, repeatable at 2 and 6 hours, with a total daily maximum of **30 mg** across all routes.
- Zyprexa Relprevv is **150-300 mg IM every 2 weeks** or 405 mg every 4 weeks, and requires 3 hours of post-injection observation.
- Start at **5 mg/day** in debilitated patients, hepatic impairment, or older adults, and taper gradually to avoid cholinergic rebound.

MECHANISM OF ACTION

- Antagonist at dopamine **D2** and serotonin **5-HT2A** receptors with a moderate D2 occupancy window that yields efficacy with limited extrapyramidal risk.
- Very high histamine **H1** affinity produces sedation and powerful appetite stimulation, the main driver of its weight gain.
- Potent 5-HT2C antagonism further increases appetite and, with H1 blockade, explains the largest metabolic burden in routine practice.
- Substantial muscarinic blockade gives dry mouth, constipation, and low extrapyramidal symptoms, but also cognitive dulling in older adults.
- Alpha-1 antagonism contributes to orthostatic hypotension, most apparent with the intramuscular formulation and rapid titration.

PHARMACOKINETICS

- Well absorbed orally, unaffected by food, with an orally disintegrating form useful when adherence or covert nonadherence is in question.
- Cleared by direct **UGT1A4** glucuronidation and by **CYP1A2** oxidation, with CYP2D6 playing only a minor role.
- Half-life averages about **30 hours** with a range of 21-54 hours, allowing once-daily dosing and reaching steady state in about a week.
- Smoking induces CYP1A2 and lowers levels, so smokers often need higher doses and levels rise sharply when a patient quits or is hospitalized.
- Women and older adults clear the drug more slowly, and clearance is about 30 percent lower in nonsmoking women than in smoking men.

ADVERSE EFFECTS

- Weight gain is the defining problem, averaging **5-7 kg** in the first months and continuing for a year or more, with high rates of clinically significant gain.
- Fasting glucose, triglycerides, and total cholesterol rise substantially, and new-onset diabetes and diabetic ketoacidosis are reported.
- Sedation, dizziness, dry mouth, constipation, and orthostatic hypotension are common and reflect H1, muscarinic, and alpha-1 blockade.
- Extrapyramidal symptoms and prolactin elevation are modest compared with risperidone, and akathisia is much less common than with aripiprazole.
- Neuroleptic malignant syndrome, seizures, and severe drug reaction with eosinophilia and systemic symptoms are rare but serious.
- Post-injection delirium and sedation syndrome occurs in about 0.07 percent of Relprevv injections and mandates supervised observation.

MONITORING

- Weight and BMI at baseline, every visit for 3 months, then quarterly; a rise above **5 percent** of body weight warrants a change in plan.
- Fasting glucose or A1c and a lipid panel at baseline, at 12 weeks, and at least annually, with earlier repeat in anyone gaining weight.
- Blood pressure at baseline and after dose changes, and orthostatic vitals when using the intramuscular formulation.
- Consider metformin coverage early rather than late in patients gaining weight who cannot switch off olanzapine.
- Track smoking status, since starting or stopping cigarettes changes CYP1A2 induction and shifts olanzapine levels markedly.

INTERACTIONS & CAUTIONS

- **Fluvoxamine** is a strong CYP1A2 inhibitor and can nearly double olanzapine levels, often requiring a dose reduction.
- **Carbamazepine** and cigarette smoke induce CYP1A2 and reduce olanzapine exposure by roughly half in heavy smokers.
- Parenteral benzodiazepines given with intramuscular olanzapine have caused fatal respiratory depression, so separate the administrations.
- Additive sedation, orthostasis, and anticholinergic load with opioids, benzodiazepines, alcohol, and antihistamines.
- Olanzapine antagonizes levodopa and dopamine agonists and is a poor choice for psychosis in Parkinson disease.

SPECIAL POPULATIONS

- One of the better characterized antipsychotics in pregnancy, though third-trimester exposure risks neonatal extrapyramidal and withdrawal signs.
- Relative infant dose in lactation is around 1 percent; breastfeeding is generally acceptable with monitoring for infant sedation.
- Approved from age 13, but adolescents show greater weight gain, sedation, and lipid elevation, so it is rarely a first-line pediatric choice.
- In older adults start at **2.5-5 mg/day** and expect anticholinergic and orthostatic effects; it is not approved for dementia-related psychosis.
- No renal adjustment is needed; in hepatic impairment start low, and monitor transaminases when they are already elevated.

PRESCRIBING PEARLS

- Reserve it for patients who need efficacy above all, and plan metabolic protection from day one.
- Smoking cessation can raise olanzapine levels enough to cause new sedation and extrapyramidal signs.
- IM olanzapine plus IM benzodiazepine has caused fatal respiratory depression; do not stack them.

References

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NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.