Olanzapine (Zyprexa)

FDA Indications:

- Schizophrenia, ages 13 and older (oral)
- Bipolar I disorder – acute manic or mixed episodes, ages 13 and older (oral, monotherapy and adjunct)
- Bipolar I disorder – maintenance treatment (adults)
- Agitation associated with schizophrenia or bipolar mania (short-acting IM, adults)
- Treatment-resistant depression in combination with fluoxetine

Off-label Use:

- Early-onset psychosis/schizophrenia
- Behavioral disturbance (irritability, aggression) in autism spectrum disorder
- Severe mood dysregulation
- Augmentation in refractory OCD
- PTSD with insomnia and hyperarousal
- Anorexia nervosa (weight restoration support)
- Delirium-related agitation

Mechanism of Action:

- Potent antagonist at D2 receptors (reduces positive psychotic symptoms)
- Strong antagonist at 5-HT2A receptors (improves negative symptoms, lowers EPS risk)
- Strong H1 antagonism (sedation, appetite increase, weight gain)
- Muscarinic M1–M5 antagonism (anticholinergic effects, metabolic effects)
- Alpha-1 antagonism (orthostatic hypotension)
- Relatively rapid D2 dissociation may reduce EPS compared to first-generation agents

Dosage Forms:

- Tablets: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg
- Orally disintegrating tablets (Zydis): 5 mg, 10 mg, 15 mg, 20 mg
- Short-acting IM injection (10 mg vial)

Dosing Guidelines (Children & Adolescents):

- Start 2.5–5 mg daily
- Increase by 2.5–5 mg increments every 1 week as tolerated
- Suggested daily range: 5–20 mg/day
- Bedtime dosing recommended to reduce daytime sedation

Pharmacology:

- Peak plasma level: approximately 5–8 hours (oral)

- Elimination half-life: 21–54 hours (longer in adolescents and nonsmokers)
- Metabolized primarily by CYP1A2; minor pathway CYP2D6
- Smoking induces CYP1A2 and may lower serum concentrations
- Does not significantly inhibit major CYP enzymes

Side Effects:

- Greater than 20% risk: significant weight gain, increased appetite, sedation
- Greater than 10% risk: hyperglycemia, dyslipidemia, orthostatic hypotension, constipation, dry mouth
- Greater than 2% risk: elevated liver enzymes, tremor, akathisia
- Less than 2% risk: QTc prolongation, neuroleptic malignant syndrome, seizures, blood dyscrasias
- Lower prolactin elevation risk compared to risperidone
- Moderate EPS risk (dose dependent)

Clinical Pearls:

- Before starting: obtain baseline weight, BMI, waist circumference, blood pressure, fasting glucose, fasting lipid profile
- After starting: BMI monthly x3 months, then quarterly
- Repeat fasting glucose and lipid panel at 3 months, then annually
- Monitor closely for rapid weight gain in adolescents
- Consider alternative agents in patients with obesity or strong metabolic family history
- One of the most metabolically burdensome second-generation antipsychotics
- Often highly effective for severe agitation and psychosis when other agents fail

References:

- Elbe D, et al. Clinical Handbook of Psychotropic Drugs for Children and Adolescents.
- Stahl SM. Stahl's Essential Psychopharmacology: Prescriber's Guide – Children and Adolescents.
- AACAP Practice Parameter for the Use of Atypical Antipsychotic Medications in Children and Adolescents.