SECOND-GENERATION ANTIPSYCHOTIC

Aripiprazole

Abilify, Abilify Maintena, Abilify Asimtufii, Aristada, Abilify MyCite

Dopamine D2 partial agonist used across psychosis, mania, and depression augmentation; low metabolic burden but high akathisia.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
10-30 mg/day PO	75 h (94 h dehydro-)	CYP2D6, CYP3A4	1-2 wks; 4-6 wks full

⚠ FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis; aripiprazole is not approved for that use. Antidepressants increased the risk of suicidal thoughts and behaviors in children, adolescents, and young adults; monitor closely for clinical worsening and emergent suicidality.

INDICATIONS

- Schizophrenia in adults and adolescents ages 13-17, and acute manic or mixed episodes of bipolar I as monotherapy or adjunct to lithium or valproate from age 10 upward.
- Adjunctive treatment of major depressive disorder in adults with inadequate response to an antidepressant, usually effective at **2-15 mg/day**.
- Irritability associated with autistic disorder in children ages 6-17, and Tourette's disorder in patients ages 6-18.
- Maintenance treatment of bipolar I disorder in adults, with long-acting injectable forms approved for schizophrenia and bipolar I maintenance.
- Off-label augmentation for obsessive-compulsive disorder, and off-label use to reverse antipsychotic-induced hyperprolactinemia while continuing the offending agent.

DOSING & TITRATION

- Schizophrenia in adults: start **10-15 mg/day PO** once daily with a usual target of **10-15 mg/day** and a labeled maximum of **30 mg/day**.
- Bipolar mania: start **15 mg/day** as monotherapy or **10-15 mg/day** as adjunct; pediatric patients start at **2 mg/day** with slow weekly steps.
- MDD augmentation: start **2-5 mg/day** and titrate by 5 mg at intervals of one week or more, to a labeled maximum of **15 mg/day**.
- Halve the dose with a strong CYP3A4 or CYP2D6 inhibitor, reduce to a quarter with both, and double it with a strong CYP3A4 inducer.
- Long-acting injectables include Abilify Maintena **300-400 mg IM monthly**, Abilify Asimtufii **720-960 mg IM every 2 months**, and Aristada every 4-8 weeks.
- No adjustment is needed for renal or hepatic impairment, and the long half-life provides a self-taper so abrupt stopping is usually tolerated.

MECHANISM OF ACTION

- Partial agonist at dopamine **D2** and **D3** receptors, acting as a functional antagonist where dopamine tone is high and an agonist where it is low.
- Partial agonism at serotonin **5-HT1A** receptors contributes to anxiolytic and antidepressant effect and blunts extrapyramidal liability.
- Potent **5-HT2A** antagonism supports activity against negative and affective symptoms and further reduces motor side effects.
- Weak histamine H1 and muscarinic blockade explains the low sedation, low weight gain, and minimal anticholinergic burden seen in practice.
- D2 partial agonism lowers prolactin below baseline rather than raising it, and also drives the characteristic early akathisia and activation.

PHARMACOKINETICS

- Oral bioavailability is about 87 percent and absorption is not clinically affected by food, although a high-fat meal delays the peak.
- Metabolized by **CYP2D6** and **CYP3A4** to dehydro-aripiprazole, an active metabolite that carries roughly 40 percent of systemic exposure.
- Terminal half-life is about **75 hours**, rising to about **94 hours** in CYP2D6 poor metabolizers, so steady state takes roughly two weeks.
- The long half-life makes an occasional missed dose forgiving, but also means every dose change needs 10-14 days before it can be judged.
- Not a clinically meaningful CYP inhibitor or inducer, and renal excretion of unchanged drug is under 1 percent of the dose.

ADVERSE EFFECTS

- Akathisia is the signature adverse effect at roughly **10-25 percent**, dose related, and frequently misread as worsening anxiety or agitation.
- Insomnia, headache, nausea, and inner restlessness are common early, concentrated in the first two weeks and often improving with dose reduction.
- Metabolic burden is among the lowest in the class, with mean weight gain usually under **2 kg** and little change in fasting glucose or lipids.
- Impulse control problems such as pathological gambling, hypersexuality, binge eating, and compulsive shopping are a labeled and reversible risk.
- Tardive dyskinesia and neuroleptic malignant syndrome occur but less often than with high-potency first-generation antipsychotics.
- Prolactin usually falls below baseline, so galactorrhea and amenorrhea are far less common than with risperidone or paliperidone.

MONITORING

- Baseline weight, BMI, waist circumference, blood pressure, fasting glucose or A1c, and a lipid panel, repeated at 12 weeks and then annually.
- Weigh at every visit for the first three months; a gain above **5 percent** of body weight should prompt intervention or a switch.
- Assess for akathisia at each early visit, ideally with the Barnes Akathisia Rating Scale, because patients report it as anxiety rather than movement.
- AIMS examination at baseline and every 6-12 months, or every 6 months in patients at elevated risk of tardive dyskinesia.
- Ask directly at each visit about new gambling, spending, eating, or sexual urges, since patients almost never volunteer them.

INTERACTIONS & CAUTIONS

- Strong **CYP2D6** inhibitors including fluoxetine, paroxetine, bupropion, and quinidine raise exposure and call for a **50 percent** dose reduction.
- Strong **CYP3A4** inhibitors such as ketoconazole, clarithromycin, and ritonavir likewise require halving the aripiprazole dose.
- **Carbamazepine** and other strong CYP3A4 inducers can halve exposure; double the dose, then retitrate downward when the inducer stops.
- Additive sedation and orthostasis with benzodiazepines, opioids, and alcohol; QT effect is negligible relative to ziprasidone or iloperidone.
- Contraindicated only in known hypersensitivity, and best avoided as an antipsychotic choice in Parkinson disease psychosis.

SPECIAL POPULATIONS

- Third-trimester exposure risks neonatal extrapyramidal signs and withdrawal; enroll exposed pregnancies in the National Pregnancy Registry for Atypical Antipsychotics.
- Relative infant dose in lactation is low, but monitor the breastfed infant for sedation and poor feeding, especially in preterm infants.
- Approved from age 6 for autism-related irritability; children require slower titration and show more sedation and weight gain than adults.
- In older adults start at **2-5 mg/day**, watch for falls and sedation, and remember the drug is not approved for dementia-related psychosis.
- No dose adjustment for renal impairment including hemodialysis, or for mild to severe hepatic impairment.

PRESCRIBING PEARLS

- Akathisia is dose related; lower the dose before adding propranolol or a benzodiazepine.
- Best metabolic profile in the class, so favor it when weight or glucose is the limiting problem.
- A 75-hour half-life means a dose change needs two weeks to judge; do not chase it early.

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.