SECOND-GENERATION ANTIPSYCHOTIC

Cariprazine

Vraylar

D3-preferring partial agonist covering mania, bipolar depression, and adjunctive MDD; very long-acting metabolites shape its use.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
1.5-6 mg/day PO	1 wk; DDCAR 1-3 wks	CYP3A4 (CYP2D6 minor)	1-2 wks; 4 wks to steady

⚠ FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis; cariprazine is not approved for that use. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients; monitor closely for worsening and emergent suicidality.

INDICATIONS

- Schizophrenia in adults and in pediatric patients ages 13-17, for acute treatment and for continued maintenance.
- Acute manic or mixed episodes of bipolar I disorder in adults and in pediatric patients ages 10-17.
- Depressive episodes associated with bipolar I disorder in adults, where it is one of a small number of approved options.
- Adjunctive therapy to antidepressants for major depressive disorder in adults with inadequate response to the antidepressant alone.
- Off-label interest centers on predominant negative symptoms of schizophrenia, supported by a positive comparison against risperidone.

DOSING & TITRATION

- Schizophrenia in adults: start **1.5 mg once daily**, may increase to 3 mg on day 2, usual range 1.5-6 mg/day, maximum **6 mg/day**.
- Bipolar mania in adults: start **1.5 mg/day**, increase to 3 mg on day 2, with an effective range of 3-6 mg/day and a 6 mg/day maximum.
- Bipolar depression and adjunctive major depressive disorder in adults: start **1.5 mg/day**, target 1.5 or 3 mg/day, maximum **3 mg/day**.
- Pediatric schizophrenia ages 13-17 and bipolar mania ages 10-17 start at **0.5 mg/day**, with a maximum of **4.5 mg/day**.
- Halve the dose when a strong **CYP3A4** inhibitor is added; concomitant strong CYP3A4 inducers are not recommended.
- Taper is rarely necessary given the long metabolite half-life, but reassess several weeks after any change before concluding it failed.

MECHANISM OF ACTION

- Partial agonist at dopamine **D3** and **D2** receptors with roughly tenfold higher affinity for D3, a profile unique among marketed agents.
- D3 preference is proposed to underlie effects on negative symptoms, anhedonia, and cognition beyond positive symptom control.
- Partial agonism at serotonin **5-HT1A** and antagonism at **5-HT2B** and 5-HT2A add antidepressant and anxiolytic activity.
- Low histamine H1 and negligible muscarinic affinity keep sedation, weight gain, and anticholinergic effects modest.
- Partial D2 agonism means prolactin does not rise, but it also drives the akathisia and insomnia seen during titration.

PHARMACOKINETICS

- Absorption is unaffected by food, so the capsule can be taken with or without meals at any consistent time of day.
- Metabolized primarily by **CYP3A4** to desmethyl and didesmethyl cariprazine, both active, with didesmethyl the dominant circulating species.
- The didesmethyl metabolite has a half-life of **1-3 weeks**, giving an effective total half-life near one week and steady state at about 4 weeks.
- Because of this, dose changes take weeks to express fully and adverse effects can persist for weeks after stopping.
- Not recommended when creatinine clearance is below **30 mL/min** or in severe hepatic impairment, where data are absent.

ADVERSE EFFECTS

- Akathisia occurs in roughly **10-20 percent** and is dose related, most often appearing within the first two weeks of a dose step.
- Extrapyramidal symptoms including parkinsonism and tremor are more common than with quetiapine but less than with risperidone.
- Insomnia, nausea, restlessness, and constipation are frequent early effects that often settle without a dose change.
- Weight gain is modest at about **1-2 kg**, with small effects on lipids and glucose, placing it in the lower metabolic tier.
- Impulse control problems, tardive dyskinesia, neuroleptic malignant syndrome, and rare leukopenia are the serious labeled risks.
- Because active metabolites persist, adverse effects can continue for weeks after the drug is stopped.

MONITORING

- Weight, BMI, blood pressure, fasting glucose or A1c, and lipids at baseline, at 12 weeks, and annually thereafter.
- Screen for akathisia and parkinsonism at every visit during the first month and after every dose increase.
- AIMS at baseline and every 6-12 months, with the reminder that resolution after stopping may be slow given the long metabolites.
- Check renal and hepatic function at baseline, since severe impairment in either makes the drug unsuitable.
- Ask about new gambling, spending, eating, or sexual urges at follow-up, as with other dopamine partial agonists.

INTERACTIONS & CAUTIONS

- Strong **CYP3A4** inhibitors including ketoconazole, itraconazole, clarithromycin, and ritonavir require halving the cariprazine dose.
- Strong **CYP3A4** inducers such as rifampin and carbamazepine markedly lower exposure, and concomitant use is not recommended.
- Grapefruit juice should be avoided because intestinal CYP3A4 inhibition unpredictably raises exposure.
- Additive sedation with opioids, benzodiazepines, and alcohol; intrinsic QT prolongation is minimal.
- Cariprazine antagonizes dopamine agonists functionally at high dopamine tone, so avoid it in Parkinson disease psychosis.

SPECIAL POPULATIONS

- Third-trimester exposure carries the class risk of neonatal extrapyramidal and withdrawal signs, prolonged by the long-lived metabolites.
- Lactation data are absent, so monitor breastfed infants closely or choose a better-characterized antipsychotic.
- Approved from age 10 for bipolar mania and 13 for schizophrenia, with a lower **4.5 mg/day** ceiling than adults.
- In older adults start at the lowest dose and expect slower resolution of akathisia; the dementia mortality warning applies.
- Not recommended when creatinine clearance is below 30 mL/min or in severe hepatic impairment.

PRESCRIBING PEARLS

- Metabolites persist for weeks, so both benefit and akathisia lag every dose change.
- Best evidence in the class for predominant negative symptoms of schizophrenia.
- Bipolar depression and adjunctive MDD both cap at 3 mg/day, not the 6 mg schizophrenia maximum.

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.