CARIPRAZINE

THERAPEUTICS

Brands • Vraylar
see index for additional brand names

Generic? No

Class

- Neuroscience-based Nomenclature: dopamine, serotonin, norepinephrine receptor antagonist (DSN-Ran)
- Dopamine partial agonist (dopamine stabilizer, atypical antipsychotic, third-generation antipsychotic; sometimes included as a second-generation antipsychotic; also a potential mood stabilizer)

Commonly Prescribed for

(bold for FDA approved)

- **Schizophrenia**
- **Acute mania/mixed mania**
- Other psychotic disorders
- Bipolar maintenance
- Bipolar depression
- Treatment-resistant depression
- Behavioral disturbances in dementia
- Behavioral disturbances in children and adolescents
- Disorders associated with problems with impulse control

How the Drug Works

- Partial agonism at dopamine 2 receptors
- Theoretically reduces dopamine output when dopamine concentrations are high, thus improving positive symptoms and mediating antipsychotic actions
- Theoretically increases dopamine output when dopamine concentrations are low, thus improving cognitive, negative, and mood symptoms
- Preferentially binds to dopamine 3 over dopamine 2 receptors at low doses; the clinical significance is unknown but could theoretically contribute to cariprazine's efficacy for negative symptoms. D3 partial agonism could theoretically be useful for treating cognition, mood, emotions, and reward/substance use
- Cariprazine also has high affinity for the serotonin 1A (partial agonist) and 2B (antagonist) receptors
- Cariprazine has moderate affinity for serotonin 2A receptors (antagonist)

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
- Classically recommended to wait at least 4–6 weeks to determine full antipsychotic efficacy of drug, but in practice some patients may require up to 16–20 weeks to show a good response, especially on cognitive impairment and functional outcome

If It Works

- Most often reduces positive symptoms but does not eliminate them
- May reduce and eliminate acute manic symptoms
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
- Most schizophrenia patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenia 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
- 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

If It Doesn't Work

- Try one of the other atypical antipsychotics
- 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 for schizophrenia, consider higher

doses or augmentation with valproate or lamotrigine
- Consider lithium and anticonvulsant mood stabilizers for mania
- 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
- Consider presence of concomitant drug abuse

Best Augmenting Combos for Partial Response or Treatment Resistance

- Valproic acid (valproate, divalproex, divalproex ER)
- Lamotrigine
- Lithium
- Benzodiazepines

Tests

Before starting any 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 mmHg)
  - 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 any 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

✻ Even 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 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 cariprazine should be discontinued at the first sign of decline in WBC in the absence of other causative factors

SIDE EFFECTS

How Drug Causes Side Effects

- Partial agonist actions at dopamine 2 receptors in the striatum can cause motor side effects, such as akathisia (occasionally)
- Partial agonist actions at dopamine 2 receptors can also cause nausea, occasional vomiting, and activating side effects
- Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown

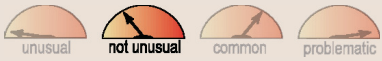
Notable Side Effects

- Akathisia, extrapyramidal symptoms, restlessness
- Gastrointestinal distress
- Sedation
- Theoretical risk of tardive dyskinesia

Life-Threatening or Dangerous Side Effects

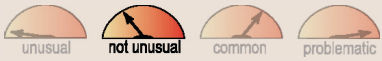
- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics)
- Rare seizures

Weight Gain



- Occurs in significant minority

Sedation



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What to Do About Side Effects

- Wait
- Wait
- Wait
- Anticholinergics or a low-dose benzodiazepine or a beta blocker may reduce akathisia effects when present
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
- Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects

- Beta blockers or sometimes benzodiazepines for akathisia
- Benztropine or trihexyphenidyl for motor side effects
- Many side effects cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range

- Schizophrenia: 1.5–6 mg once daily
- Bipolar mania: 3–6 mg once daily

Dosage Forms

- Capsule 1.5 mg, 3 mg, 4.5 mg, 6 mg

How to Dose

- Schizophrenia: initial 1.5 mg once daily; can increase to 3 mg once daily on day 2; can increase in 1.5–3 mg increments to reach therapeutic dose (recommended dose 1.5–6 mg once daily)
- Bipolar mania: initial 1.5 mg once daily; can increase to 3 mg once daily on day 2; can increase in 1.5–3 mg increments to reach therapeutic dose (recommended dose 3–6 mg once daily)

Dosing Tips

- Because of its long half-life, and the especially long half-life of one of its active metabolites, monitor for adverse effects and response for several weeks after starting cariprazine and with each dosage change; also washout of active drug will take several weeks
- Because of its long half-life, missing a few doses may not be as detrimental compared to other antipsychotics
- Can be taken with or without food

Overdose

- Limited experience

Long-Term Use

- Not extensively studied, but long-term maintenance treatment is often necessary for schizophrenia and bipolar mania
- Should periodically reevaluate long-term usefulness in individual patients, but treatment may need to continue for many years in patients with schizophrenia

Habit Forming

- No

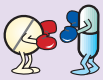
How to Stop

- Because clinical experience is lacking, down-titration may be prudent, especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- However, the long half-lives of cariprazine and its two active metabolites suggest that it may be possible to stop cariprazine abruptly

- The method for stopping cariprazine can vary depending on which agent is being switched to; see switching guidelines of individual agents for how to stop cariprazine
- Rapid discontinuation could theoretically lead to rebound psychosis and worsening of symptoms, but less likely with cariprazine due to its long half-life

Pharmacokinetics

- Metabolized by CYP450 3A4 into two long-lasting active metabolites
- Based on time to reach steady state, half-life for cariprazine is 2–4 days and for one of its active metabolites, didesmethyl cariprazine (DDCAR), is 1–3 weeks



Drug Interactions

- Initiating a strong CYP450 3A4 inhibitor in patients on a stable dose of cariprazine: reduce the current dose of cariprazine by half (for patients taking 4.5 mg, reduce to either 1.5 mg or 3 mg once daily; for patients taking 1.5 mg once daily, reduce to 1.5 mg every other day)
- Initiating cariprazine in patients taking a strong CYP450 3A4 inhibitor: administer 1.5 mg on day 1; do not dose on day 2; administer 1.5 mg on day 3 and on day 4; maximum dose 3 mg once daily
- Concomitant use of cariprazine and a CYP450 3A4 inducer is not recommended
- May increase effects of antihypertensive agents
- May antagonize levodopa, dopamine agonists

Other Warnings/ Precautions

- Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
- Dysphagia has been associated with antipsychotic use, and cariprazine should be used cautiously in patients at risk for aspiration pneumonia

Do Not Use

- If there is a proven allergy to cariprazine

SPECIAL POPULATIONS

Renal Impairment

- Mild to moderate impairment (creatinine clearance <30 mL/minute): no dose adjustment necessary
- Severe or end-stage: not recommended

Hepatic Impairment

- Mild to moderate impairment (Child-Pugh score between 5 and 9): no dose adjustment necessary
- Severe: not recommended

Cardiac Impairment

- Use in patients with cardiac impairment has not been studied, so use with caution

Elderly

- Some elderly patients may tolerate lower doses better
- 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

- Safety and efficacy have not been established
- Children and adolescents using cariprazine may need to be monitored more often than adults

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

- In rats, administration of cariprazine during organogenesis caused malformations, lower pup survival, and developmental delays at exposures less than the human exposure at maximum recommended human dose (6 mg/day); cariprazine was not teratogenic in rabbits at doses up to 4.6 times the maximum recommended human dose
- 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
- National Pregnancy Registry for Atypical Antipsychotics: 1-866-961-2388 or http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/

Breast Feeding

- Unknown if cariprazine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- ✻ Recommended either to discontinue drug or bottle feed unless the potential benefit to the mother justifies the potential risk to the child
- Infants of women who choose to breast feed while on cariprazine should be monitored for possible adverse effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- For patients who do not tolerate aripiprazole or brexpiprazole
- Possibly negative symptoms in schizophrenia

Potential Disadvantages

- Expensive

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Symptoms of acute mania/mixed mania
- Cognitive symptoms
- Unstable mood (both depression and mania)
- Aggressive symptoms

Pearls

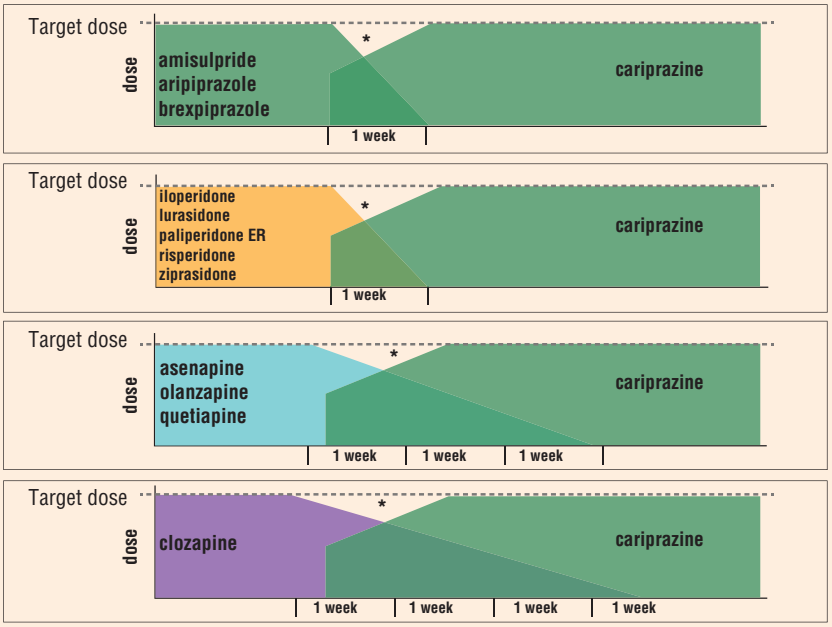
- Cariprazine is metabolized into a very long-lasting active metabolite; it is therefore possible that adverse events could appear several weeks after initiation of cariprazine due to accumulation of cariprazine and major metabolites over time
- It is also possible that cariprazine or its very long-lasting active metabolites could be developed as an "oral depot" namely, a very long-lasting oral formulation for weekly or even monthly oral administration
- Based on short-term clinical trials, cariprazine appears to have a favorable metabolic profile, with changes in triglycerides, fasting glucose, and cholesterol similar to placebo; however, it may cause a small amount of dose-dependent weight gain
- Cariprazine is also being studied for the treatment of bipolar depression and as an adjunct for treatment-resistant unipolar depression
- D3-preferring (over D2) actions represent a novel pharmacologic profile among antipsychotics, especially at lower doses; clinical advantages of this profile remain to be determined but animal models suggest that targeting D3 receptors may have advantages for mood, negative symptoms, and substance abuse
- All antipsychotics bind to the D3 receptor in vitro, but only cariprazine has affinity for the D3 receptor greater than dopamine itself, so it is the only antipsychotic with functional D3 partial agonism in vivo in the living human brain

THE ART OF SWITCHING

Switching from Oral Antipsychotics to Cariprazine

- It is advisable to begin cariprazine at an intermediate dose and build the dose rapidly over 3–7 days
- Clinical experience has shown that asenapine, quetiapine, and olanzapine should be tapered off slowly over a period of 3–4 weeks, to allow patients to readapt to the withdrawal of blocking cholinergic, histaminergic, and alpha 1 receptors
- Clozapine should always be tapered off slowly, over a period of 4 weeks or more

* Benzodiazepine or anticholinergic medication can be administered during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis



Suggested Reading

Choi YK, Adham N, Kiss B, Gyertyán I, Tarazi FI. Long-term effects of cariprazine exposure on dopamine receptor subtypes. CNS Spectr 2014;19(3):268–77.

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