U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Cariprazine. [Updated 2017 Jun 1].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Cariprazine

Updated: June 1, 2017.

OVERVIEW

Introduction

Cariprazine is an atypical antipsychotic used in the treatment of schizophrenia and manic or mixed episodes of bipolar disorder. Cariprazine has been associated with a low rate of serum aminotransferase elevations during therapy, but it has not been linked to instances of clinically apparent acute liver injury.

Background

Cariprazine (kar ip' ra zeen) is an atypical antipsychotic which appears to act as a partial agonist of dopamine type 2 (D2) and 3 (D3) receptors. The D2 and D3 receptors have been identified as targets for therapy of schizophrenia where they appear to be overstimulated. Cariprazine also may have some degree of activity against selected serotonin receptors (5-HT1A). In short term clinical trials, cariprazine was shown to improve symptoms in patients with schizophrenia and manic or mixed episodes of bipolar I disorder. Cariprazine was approved for these indications in the United States in 2015 and is available in capsules of 1.5, 3, 4.5 and 6 mg under the brand name Vraylar. The recommended initial dose is 1.5 mg once daily, with subsequent dose increases based upon efficacy and tolerance to 3 to 6 mg daily. Common side effects include dizziness, sedation, somnolence, nausea, weight gain, restlessness, tremor, akathisia and extrapyramidal symptoms. More serious adverse events can include cerebrovascular events such as transient ischemic attacks, particularly in the elderly with dementia, neurologic malignant syndrome, marked weight gain, dyslipidemia, diabetes, and orthostatic hypotension.

Hepatotoxicity

Serum aminotransferase elevations above 3 times the upper limit of normal occurred in 2% to 4% of patients treated with cariprazine in preregistration studies compared with 0.7% to 2% of placebo recipients. Elevations above 5 times ULN were rare <1% and no patient developed clinically apparent liver injury with jaundice or symptoms. Nevertheless, an occasional patient was withdrawn from therapy because of serum aminotransferase elevations usually arising within the first month of treatment and resolving rapidly with drug discontinuation. Since its approval and more widescale use, there have been no published cases of clinically apparent liver injury although the product label lists hepatitis as a possible adverse side effect.

Likelihood score: E* (unproven but suspected rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which cariprazine causes serum aminotransferase elevations is not known, but is likely due to production of a toxic intermediate by its metabolism. Cariprazine is extensively metabolized by the liver via CYP

3A4 and is susceptible to drug-drug interactions with inhibitors or inducers of CYP 3A. Some instances of mild serum aminotransferase elevations occurring on cariprazine therapy may be due to nonalcoholic fatty liver disease caused by weight gain that generally occurs during the first 1 to 2 years of therapy.

Outcome and Management

The serum aminotransferase elevations that occur on cariprazine therapy are usually self-limited and usually do not require dose modification or discontinuation of therapy. Elevations of serum ALT or AST above 5 times the upper limit of normal or any elevations accompanied by jaundice or symptoms should prompt temporary discontinuation until the clinical course of the injury and role of the drug are better defined. Cariprazine has not been implicated in cases of acute liver failure, chronic liver injury or vanishing bile duct syndrome. There is no evidence to suggest cross sensitivity to liver injury between cariprazine and other atypical antipsychotic agents.

Drug Class: Antipsychotic Agents, Atypicals

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Cariprazine – Vraylar®

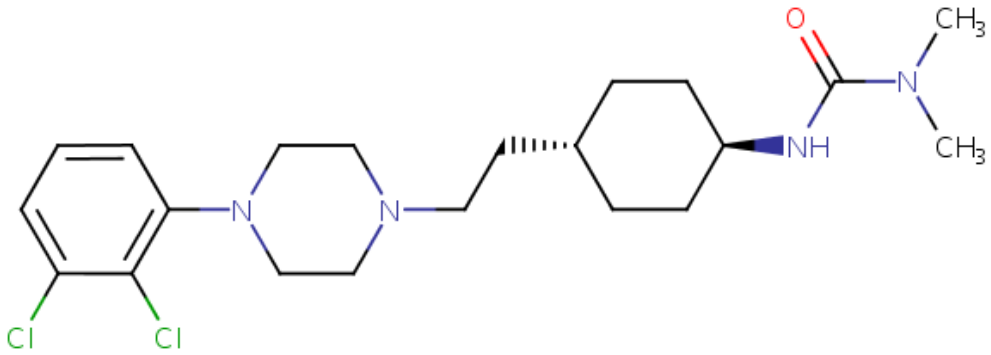
DRUG CLASS

Antipsychotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Cariprazine	839712-12-8	C21-H32-Cl2-N4-O	

ANNOTATED BIBLIOGRAPHY

References updated: 01 June 2017

Meyer JM. Pharmacotherapy of psychosis and mania. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 417-56.

(Textbook of pharmacology and therapeutics).

Durgam S, Starace A, Li D, Migliore R, Ruth A, Németh G, Laszlovszky I. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. Schizophr Res 2014;152: 450-7. PubMed PMID: 24412468.

(Among 732 adults with an acute exacerbation of schizophrenia treated with cariprazine [1.5, 3.0 and 4.5 mg] or risperidone [4 mg] or placebo daily for 6 weeks, improvement in symptom scores occurred in all treatment

groups, and side effects that were more frequent with cariprazine than placebo were insomnia, extrapyramidal symptoms, akathisia, sedation, nausea, dizziness and constipation, while mean levels of ALT increased slightly [0.8 to 3.2 U/L] in a dose dependent manner with cariprazine, however there were no cases of clinically apparent liver injury).

Durgam S, Cutler AJ, Lu K, Migliore R, Ruth A, Laszlovszky I, Németh G, et al. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. J Clin Psychiatry 2015; 76: e1574-82. PubMed PMID: 26717533.

(Among 617 patients with schizophrenia treated with cariprazine [3 or 6 mg], aripiprazole [10 mg] or placebo daily for 6 weeks, symptoms improved with cariprazine and aripiprazole compared to placebo, and side effects included insomnia, akathisia and headache).

Calabrese JR, Keck PE Jr, Starace A, Lu K, Ruth A, Laszlovszky I, Németh G, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. J Clin Psychiatry 2015; 76: 284-92. PubMed PMID: 25562205.

(Among 497 patients with acute and mixed mania due to bipolar I disorder treated with cariprazine or placebo for 3 weeks, mean serum ALT levels rose slightly [4-5 U/L vs 1 U/L with placebo], but mean AST, alkaline phosphatase or bilirubin values did not).

Kane JM, Zukin S, Wang Y, Lu K, Ruth A, Nagy K, Laszlovszky I, et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: results from an international, phase III clinical trial. J Clin Psychopharmacol 2015; 35: 367-73. PubMed PMID: 26075487.

(Among 446 patients with an acute exacerbation of schizophrenia treated with cariprazine [3-9 mg] or placebo daily for 6 weeks, symptoms improved with cariprazine therapy and adverse events included akathisia, extrapyramidal symptoms and tremor, while ALT elevations above 3 times ULN occurred in 1% of all 3 groups, but led to discontinuation in 1 cariprazine treated subject).

Sachs GS, Greenberg WM, Starace A, Lu K, Ruth A, Laszlovszky I, Németh G, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. J Affect Disord 2015; 174: 296-302. PubMed PMID: 25532076.

(Among 312 patients with acute manic or mixed episodes due to bipolar I disorder treated with cariprazine [3-12 mg daily] or placebo for 3 weeks, symptom scores improved more with cariprazine while side effects included extrapyramidal symptoms, akathisia, tremor, dyspepsia and vomiting and mean changes in ALT levels were 13 vs 7 U/L; no mention of hepatotoxicity or liver related reason for discontinuation or dose modification).

McCormack PL. Cariprazine: First global approval. Drugs 2015; 75: 2035-43. PubMed PMID: 26510944.

(Review of the mechanism of action, pharmacology, clinical efficacy and safety of cariprazine as therapy for schizophrenia and manic or mixed episodes of bipolar I disorder; mentions that cariprazine has been associated with a higher rate of liver enzyme elevations compared to placebo, but that no clinically apparent liver injury with jaundice occurred).

Durgam S, Earley W, Lipschitz A, Guo H, Laszlovszky I, Németh G, Vieta E, et al. An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. Am J Psychiatry 2016; 173: 271-81. PubMed PMID: 26541814.

(Among 571 patients with acute manic or mixed episodes due to bipolar I disorder treated with cariprazine [0.75, 1.5 and 3 mg daily] or placebo for 6 weeks, symptom scores improved more with cariprazine and side effects included akathisia, insomnia and weight gain; there were minimal changes in serum ALT and AST values and no instance of clinically apparent liver injury with jaundice).

Durgam S, Earley W, Li R, Li D, Lu K, Laszlovszky I, Fleischhacker WW, et al. Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: A randomized, double-blind, placebo-controlled trial. Schizophr Res 2016; 176: 264-71. PubMed PMID: 27427558.

(Among 200 patients with schizophrenia enrolled in an open label treatment study who were continued on cariprazine or placebo for up to 97 weeks, relapses occurred in 25% of cariprazine vs 48% of placebo recipients and there were slight increases in mean ALT levels, one patient developing ALT elevations and jaundice during cariprazine therapy).

Cariprazine (Vraylar) for schizophrenia and bipolar I disorder. Med Lett Drugs Ther 2016; 58 (1493): 51-3. PubMed PMID: 27101209.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of cariprazine shortly after its approval for use in the US; mentions side effects of extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, restlessness and weight gain, but not ALT elevations or hepatotoxicity).

Németh G, Laszlovszky I, Czobor P, Szalai E, Szatmári B, Harsányi J, Barabássy Á, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. Lancet 2017; 389 (10074): 1103-13. PubMed PMID: 28185672.

(Among 461 adults with stable schizophrenia treated with cariprazine [3-6 mg] or risperidone [3-6 mg] daily for 26 weeks, symptom scores improved more with cariprazine and rates of adverse events were similar, mean ALT and AST levels changing minimally in both groups).

Earley W, Durgam S, Lu K, Debelle M, Laszlovszky I, Vieta E, Yatham LN. Tolerability of cariprazine in the treatment of acute bipolar I mania: A pooled post hoc analysis of 3 phase II/III studies J Affect Disord 2017; 215: 205-12. PubMed PMID: 28343051.

(Among 1065 patients with acute mania or mixed episode of bipolar I disorder treated with cariprazine or placebo for 3 weeks, adverse events more frequent with active treatment included akathisia, extrapyramidal symptoms, restlessness and vomiting; and while mean changes in ALT and AST were slightly higher with higher doses of cariprazine, there were no instances of clinically apparent liver injury with jaundice).

Durgam S, Greenberg WM, Li D, Lu K, Laszlovszky I, Nemeth G, Migliore R, et al. Safety and tolerability of cariprazine in the long-term treatment of schizophrenia: results from a 48-week, single-arm, open-label extension study. Psychopharmacology (Berl) 2017; 234: 199-209. PubMed PMID: 27807604.

(Among 93 patients who had a response during a 6 week controlled trial and were continued on cariprazine [1.5 to 4.5 mg/day] for another 48 weeks, side effects included akathisia, insomnia and weight gain and 13% of patients had a serious adverse event, but there were no "clinically meaningful changes from baseline" in liver tests and no discontinuation was attributed to liver injury).