

The Medical Letter[®]

on Drugs and Therapeutics

Volume 66

Published online June 10, 2024

Advance
Release
Article

IN THIS ISSUE

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IN BRIEF

Iloperidone (*Fanapt*) – A New Indication for Bipolar Disorder

Iloperidone (*Fanapt* – Vanda), an oral second-generation antipsychotic drug, has been approved by the FDA for acute treatment of manic or mixed episodes associated with bipolar I disorder in adults. First approved in 2009 for treatment of schizophrenia, iloperidone is the eighth second-generation antipsychotic to be approved for acute treatment of manic or mixed episodes of bipolar I disorder (see Table 1).

TREATMENT OF MANIA – Bipolar I disorder is characterized by a history of at least one manic episode with or without a history of depression. Lithium, valproate, carbamazepine, and second-generation antipsychotic drugs are effective for

treatment of acute manic episodes, but lithium and valproate may take days to weeks to have a full therapeutic effect. Second-generation antipsychotic drugs can be used as monotherapy or in combination with lithium or valproate.^{1,2}

CLINICAL STUDIES – FDA approval of iloperidone for the new indication was based on the results of a double-blind trial in 392 patients with bipolar mania, with or without mixed features, who were randomized to receive iloperidone or placebo twice daily for 4 weeks. The least-squares mean change from baseline to week 4 in the Young Mania Rating Scale (measures irritability, speech, thought content, disruptive/aggressive behavior, etc.), the primary endpoint, was statistically significantly greater with iloperidone than with placebo (-14.0 vs -10.0; mean score at baseline = 29).³

Table 1. FDA-Approved Indications of Second-Generation Antipsychotic Drugs for Bipolar Disorder

Drug	Acute Treatment of Bipolar I ¹ Manic or Mixed Episodes	Bipolar I ¹ Depression	Bipolar II ² Depression	Maintenance Treatment
Aripiprazole* – immediate-release oral	Yes	No	No	No
extended-release IM	No	No	No	Yes
Asenapine sublingual*	Yes	No	No	Yes
Cariprazine oral	Yes	Yes	No	No
Iloperidone oral	Yes	No	No	No
Lumateperone oral	No	Yes	Yes	No
Lurasidone oral*	No	Yes	No	No
Olanzapine ³ oral*	Yes	No	No	Yes
Olanzapine/fluoxetine oral*	No	Yes	No	No
Olanzapine/samidorphan oral	Yes	No	No	Yes
Quetiapine* – immediate-release oral	Yes (manic only)	Yes	No	Yes
extended-release oral	Yes	Yes	No	Yes
Risperidone* – immediate-release oral	Yes	No	No	No
extended-release IM	No	No	No	Yes
Ziprasidone oral*	Yes	No	No	Yes

*Available generically; IM = intramuscular

1. At least one manic episode with or without a history of depression.

2. At least one hypomanic and one depressive episode without a history of mania.

3. Also available in a short-acting intramuscular injection for acute agitation associated with bipolar mania.

ADVERSE EFFECTS – The most common adverse effects of iloperidone in the clinical trial were tachycardia, dizziness, dry mouth, hepatic enzyme elevations, nasal congestion, weight gain, orthostatic hypotension, and somnolence. Neuroleptic malignant syndrome, akathisia, tardive dyskinesia, dyslipidemia, hyperglycemia, falls, seizures, leukopenia, neutropenia, agranulocytosis, and priapism can occur. Patients with bipolar disorder are particularly susceptible to extrapyramidal symptoms. Iloperidone can also prolong the QT interval and increase the risk of arrhythmias and sudden death.

PREGNANCY AND LACTATION – Data on use of second-generation antipsychotic drugs during pregnancy are limited; increased birth weight has been reported. Neonates whose mothers were exposed to antipsychotic drugs during the third trimester are at increased risk for extrapyramidal and withdrawal symptoms after delivery. No data are available on the presence of iloperidone in human milk or its effects on the breastfed infant or milk production. Breastfeeding is not recommended during treatment with iloperidone.

DRUG INTERACTIONS – Concomitant use of iloperidone with other drugs that prolong the QT interval or with alpha-adrenergic blockers should be avoided. The dose of iloperidone should be reduced by half in patients who are CYP2D6 poor metabolizers or are taking strong CYP2D6 or CYP3A4 inhibitors concurrently.⁴

DOSAGE, ADMINISTRATION, AND COST – Iloperidone is supplied in 1-, 2-, 4-, 6-, 8-, 10-, and 12-mg tablets.

Because of the risk of hypotension, the dosage should be increased gradually, starting with 1 mg twice daily, with daily increases to 3, 6, 9, and 12 mg twice daily thereafter. Iloperidone is not recommended for use in patients with severe hepatic impairment. The wholesale acquisition cost (WAC) for a 30-day supply of *Fanapt* at the recommended target dosage is about \$3525.⁵

CONCLUSION – In one 4-week trial, the oral second-generation antipsychotic drug iloperidone (*Fanapt*) reduced symptoms of mania associated with bipolar I disorder in adults. Antipsychotic drugs that are available generically and have a longer record of efficacy for acute treatment of manic or mixed episodes are preferred. ■

1. LN Yatham et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord* 2018; 20:97.
2. Drugs for bipolar disorder. *Med Lett Drugs Ther* 2024; 66:49.
3. R Torres et al. Efficacy and safety of iloperidone in bipolar mania: a double-blind, placebo-controlled study. *J Clin Psychiatry* 2024; 85:23m14966.
4. Inhibitors and inducers of CYP enzymes, P-glycoprotein, and other transporters. *Med Lett Drugs Ther* 2023 January 25 (epub). Available at: www.medicalletter.org/downloads/CYP_PGP_Tables.pdf.
5. Approximate WAC for one week of treatment with the lowest dose and/or longest dosing interval. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. June 5, 2024. Reprinted with permission by First Databank, Inc. All rights reserved. ©2024. www.fdbhealth.com/policies/drug-pricing-policy.

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