

Iloperidone for schizophrenia

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New treatment option for patients who have not fully responded to or cannot tolerate other antipsychotics

Iloperidone is a second-generation (atypical) antipsychotic the FDA approved in May 2009 for treating acute schizophrenia in adults (*Table 1*). Iloperidone is not a derivative (metabolite, isomer, or different formulation) of any other antipsychotic. Clinical trials have shown that iloperidone is efficacious and suggest that for some patients its side-effect profile may be more favorable than that of other antipsychotics.

Clinical implications

Iloperidone's binding profile is similar to that of other antipsychotics with relatively stronger affinity for serotonin (5-HT_{2A}) than dopamine (D₂) receptors, and its efficacy is roughly comparable to that of other non-clozapine antipsychotics.

Individual patients may respond differently to specific antipsychotics, even when those agents have shown equivalent efficacy in clinical trials. Therefore, a key therapeutic question is the degree of differential efficacy—differences in response at an individual level—among iloperidone and other antipsychotics.

The differential efficacy among iloperidone and other antipsychotics is unknown. Our clinical experience and iloperidone's unique structure suggest, however, that this agent might be helpful for certain patients who do not fully respond to or are unable to tolerate other antipsychotics.

Table 1

Iloperidone: Fast facts

Brand name: Fanapt
Class: Atypical antipsychotic (serotonin/dopamine antagonist)
Indication: Acute schizophrenia in adults
Approval date: May 2009
Availability date: Late 2009
Manufacturer: Vanda Pharmaceuticals, Inc.
Dosing forms: 1-, 2-, 4-, 6-, 8-, 10-, and 12-mg tablets (nonscored); titration pack of 2x1-mg, 2x2-mg, 2x4-mg, and 2x6-mg tablets
Starting dose: 1 mg bid (2 mg total daily dose)
Target dose: 12 to 24 mg total daily dose

How iloperidone works

Like other antipsychotics, iloperidone's efficacy presumably is based on its ability to block [antagonize] dopamine D₂ receptors. Its chemical structure is most similar to risperidone, paliperidone, and ziprasidone, but its receptor binding profile is distinguished by a relatively lower affinity for serotonin receptors 5-HT_{1A} and 5-HT_{2C} than ziprasidone, and a relative lack of muscarinic and histaminic antagonist properties (*Table 2*).

The relatively higher affinity of iloperidone (and its metabolite P95) for the NE α 1 receptor correlates with the drug's propensity to cause orthostatic hypotension

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Table 2

Relative receptor binding affinities of 3 atypical antipsychotics*

Receptor	Binding affinity		
	Risperidone	Ziprasidone	Iloperidone
Dopamine D2	High	High	High
Serotonin 5-HT1A	Low	High	Low
Serotonin 5-HT2A	High	High	High
Serotonin 5-HT2C	Moderate	High	Moderate [†]
Norepinephrine NE α 1	High	Moderate	Moderate ^{††}
Histamine H1	Moderate	Moderate	Low
Muscarinic M1	Negligible	Negligible	Negligible

*Cross-comparison of binding strengths reflects the subjective judgment of the authors. The goal is to demonstrate differences in overall binding patterns, and these estimates should not be considered an exact cross-comparison

[†]Published reports of binding affinity of iloperidone show considerable variation for the 5HT2C site

^{††}One metabolite of iloperidone [P95] does not have CNS activity but has potent alpha-1 antagonism and may contribute to the initial orthostatic hypotension seen in clinical trials

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Iloperidone’s relatively strong NE α 1 antagonism creates some risk for initial orthostatic hypotension

during initial up-titration.¹ Differences in iloperidone’s receptor binding profile compared with other antipsychotics likely are responsible for its different side-effect profile.^{2,3}

Pharmacokinetics

Iloperidone is administered twice daily and can be taken with or without food. The bioavailability of iloperidone tablets is 96%, and peak plasma concentrations are achieved 2 to 4 hours after ingestion.

Like all antipsychotics except paliperidone, iloperidone is metabolized by the liver’s cytochrome P450 (CYP) system. The enzyme pathways CYP3A4 and CYP2D6 transform iloperidone into 2 metabolites: one with CNS activity (P88) and one that does not cross the blood-brain barrier and is not active in the CNS (P95) but likely has peripheral effects.

Genetic variations in CYP2D6 activity can substantially alter how individual patients metabolize iloperidone. The half-life of iloperidone and its active metabolites differs depending on whether someone is a poor metabolizer (no functional CYP2D6 activity), intermediate metabolizer (reduced CYP2D6 activity), or extensive metabolizer (“normal” CYP2D6 activity). The usual half-life of iloperidone (approximately 18

hours in extensive metabolizers) can be almost 50% longer (>24 hours) in CYP2D6 poor metabolizers.

There are no recommendations to test patients for genetic variants that result in poor metabolism from CYP2D6. Rather, clinicians simply need to be aware that this could be the source of interindividual differences they see in iloperidone tolerability, just as it is for any other medication that is a substrate for the CYP2D6 enzyme system.

Interactions. Medications that inhibit the CYP3A4 or CYP2D6 systems can increase iloperidone plasma level when taken concurrently with iloperidone, even if intrinsic liver metabolism activity is normal. Fluoxetine and paroxetine are potent CYP2D6 inhibitors. Concurrent treatment with either of these selective serotonin reuptake inhibitors could increase iloperidone plasma concentration by 100% or more.⁴

Similarly, cotreatment with a potent CYP3A4 inhibitor such as ketoconazole (or drinking grapefruit juice) will decrease metabolism and increase plasma concentrations of iloperidone and its active metabolites by about 50%. Smoking status should not influence iloperidone plasma concentration because this drug is not a primary substrate for CYP1A2, the enzyme induced by cigarette smoking.

continued

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Reduce iloperidone dosage by 50% for patients who are taking a strong CYP2D6 or CYP3A4 inhibitor

Table 3

Common side effects: iloperidone vs other antipsychotics*

Other antipsychotic	Less likely or less severe with iloperidone	More likely or more severe with iloperidone
Haloperidol ^{4,8}	EPS Akathisia Prolactin elevation	Weight gain Orthostasis
Olanzapine	Dyslipidemia Weight gain Sedation	Orthostasis
Quetiapine	Dyslipidemia Sedation	EPS
Risperidone ^{4,6}	EPS Prolactin elevation Akathisia	None
Ziprasidone ⁷	EPS Akathisia	Weight gain Orthostasis
Aripiprazole	Akathisia	Weight gain Orthostasis

*Iloperidone has been compared head-to-head with haloperidol, risperidone, and ziprasidone in clinical trials. Other suggested antipsychotic side effect liabilities are based on indirect comparisons
EPS: extrapyramidal symptoms

The bottom line: reduce iloperidone dosage by 50% for patients who are taking a strong CYP2D6 and/or CYP3A4 inhibitor (see Dosing below).

Efficacy

In clinical trials, iloperidone was shown to be efficacious in treating positive and negative symptoms and general psychopathology in acute episodes of schizophrenia. It is important to consider the efficacy studies of iloperidone within the context of the history of its development plan.

Early clinical trials. Most of iloperidone’s phase II and III studies were conducted by Novartis between 1998 and 2002. Initial phase III studies included three 6-week, double-blind, placebo-controlled acute trials comparing a range of iloperidone doses with placebo and an active comparator:^{5,6}

- The first trial compared iloperidone, 4, 8, or 12 mg/d, with placebo or haloperidol, 15 mg/d.
- The second compared iloperidone, 4 to 8 mg/d or 10 to 16 mg/d, with placebo and risperidone, 4 to 8 mg/d.
- The third compared iloperidone, 12 to

16 mg/d or 20 to 24 mg/d, with placebo or risperidone, 6 to 8 mg/d.

These studies totaled 1,066 patients in the iloperidone treatment arms, with target dosages for iloperidone ranging from 4 to 24 mg/d. Iloperidone was more efficacious than placebo for positive, negative, and overall total symptoms on the Positive and Negative Syndrome Scale (PANSS), albeit 4 mg/d and 8 mg/d dosages narrowly missed the .05 significance level.

The haloperidol and risperidone active controls appeared more effective than iloperidone in the original analyses, but these studies were not designed for analysis of comparative efficacy. The protocols for all of these studies used an up-titration schedule for the iloperidone groups that took 1 week to reach steady-state levels, whereas the haloperidol and risperidone groups had a briefer up-titration to target dose.

The interpretation of these studies is complex and a detailed discussion is beyond the scope of this article. However, a post-hoc analysis that included subjects who remained in the study after 2 weeks of double-blind medication showed that iloperidone performed comparably to risperidone⁷ and haloperidol.⁸

A new phase III trial. The question remained whether iloperidone was as efficacious as other first-line antipsychotics but had been “penalized” by its slower up-titration schedule and clinical trial design flaws. After acquiring the development rights to iloperidone from Novartis and reviewing prior study designs and results, Vanda Pharmaceuticals designed another phase III study comparing iloperidone with placebo and ziprasidone. Its purpose was to correct for possible design flaws in the previous studies.

Ziprasidone was selected as the active control because of its established efficacy, safety, and twice-daily dosing. In this trial, researchers attempted to match the 2 drugs’ up-titration schedules. Twice-daily doses were given with food as follows:

- iloperidone, 1, 2, 4, 6, 8, 10, and 12 mg (days 1 to 7, respectively)
- ziprasidone, 20 mg (days 1 to 2), 40 mg (days 3 to 4), 60 mg (days 5 to 6), and 80 mg (day 7).

By day 7, target dosages were reached: iloperidone, 24 mg/d, and ziprasidone, 160 mg/d.⁹

Patients receiving iloperidone showed significantly greater improvement in PANSS total scores at 4 weeks vs those receiving placebo (-12.0, iloperidone; -7.1, placebo; *P* < .01).⁹ Patients receiving ziprasidone also achieved significantly greater improvement vs those receiving placebo (-12.3; *P* < .05 vs placebo).

The iloperidone and ziprasidone groups showed significantly greater improvement from baseline vs placebo in PANSS positive (P) and negative (N) subscale scores. Significantly more patients receiving iloperidone (72%) than placebo (52%) experienced improvement (≥20% reduction from baseline) in PANSS-P scores (*P* = .005).

Patients receiving iloperidone had a significantly greater reduction in Clinical Global Impression-Severity scale score vs placebo (-0.65 and -0.39, respectively; *P* =

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Clinical trials have shown comparable efficacy among iloperidone, ziprasidone, risperidone, and haloperidol



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Compared with risperidone, iloperidone has a lower liability of extrapyramidal symptoms

.007), as did patients receiving ziprasidone (-0.67 ; $P = .013$).

Iloperidone met all predefined protocol criteria for efficacy vs placebo and had efficacy equal to the highest approved dose of ziprasidone. These results demonstrated that iloperidone has comparable efficacy to ziprasidone and support the validity of the re-analysis of earlier studies showing comparable efficacy between iloperidone and risperidone⁷ or haloperidol.⁸ In July 2008 the FDA issued a not approvable letter for iloperidone, requesting further clinical trials because of concerns about the drug's efficacy compared with risperidone. The FDA approved iloperidone in May 2009 after the manufacturer provided additional data from existing trials that demonstrated comparable efficacy to risperidone.

Long-term efficacy. A double-blind extension study compared patients remaining on blinded iloperidone (4 to 16 mg/d) or haloperidol (5 to 20 mg/d) after completing a 6-week efficacy study.¹⁰ The drugs showed equivalent efficacy in preventing relapse over 46 weeks follow-up. Because this study included no placebo group, the FDA does not consider it to be an interpretable relapse prevention study.

Tolerability

Clinicians might consider iloperidone when seeking to switch a patient to an antipsychotic with a potentially lower side-effect burden.^{6,11} Compared with risperidone, iloperidone has a lower liability for extrapyramidal symptoms (EPS) and does not cause clinically significant prolactin elevation (*Table 3, page 48*).^{5,7-9} Compared with ziprasidone, iloperidone has a lower EPS and akathisia liability. Somewhat greater weight gain was seen with iloperidone when compared with ziprasidone in a 4-week study (iloperidone, +2.8 kg; ziprasidone, +1.1 kg; placebo, +0.5 kg) but the 2 drugs' effects on triglycerides and cholesterol were comparable.⁹

Iloperidone has a similar degree of QTc prolongation as ziprasidone (mean 9 msec

at the highest dosage of 12 mg bid). Safety studies including administration of maximal doses of iloperidone with CYP3A4 and CYP2D6 inhibitors showed a mean QTc prolongation of 19 msec without clinically significant problems, and iloperidone has not been associated with serious arrhythmia.⁴ Iloperidone should not be prescribed to patients with significant cardiac problems or electrolyte disturbances, however, or those taking drugs known to have clinically significant QTc/proarrhythmic properties, such as thioridazine, droperidol, pimozone, or methadone.⁴

Iloperidone has the same safety concerns associated with other atypical antipsychotics, including tardive dyskinesia and neuroleptic malignant syndrome. Like other atypical antipsychotics, iloperidone carries a warning of increased mortality risk in elderly patients with dementia-related psychosis.

Dose-related side effects include dizziness, orthostatic hypotension, and tachycardia. Dizziness occurred more often at higher doses (20% at 20 to 24 mg/d vs 10% at 10 to 16 mg/d vs 7% in placebo groups). Presumably these side effects are related to NE α 1 antagonism and are the basis for the recommended dose-titration schedule described below. Clinical trials do not seem to demonstrate a dose-response relationship for acute EPS or akathisia.

Dosing

The approved dosage range for iloperidone is 12 to 24 mg/d, given as 6 to 12 mg bid. Some trials suggest a dose-response relationship, with 24 mg being more effective than lower target doses.⁵ Reduce the target dosage of iloperidone by one-half when administering it concomitantly with medications that are strong CYP2D6 or CYP3A4 inhibitors.

Titration schedule. Because iloperidone's relatively strong NE α 1 antagonism creates risk for initial orthostatic hypotension, the drug needs to be titrated to the target dose over 4 to 7 days:

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- 1 mg bid at day 1
- 2 mg bid at day 2
- 4 mg bid at day 3
- 6 mg bid at day 4 (for a target dosage of 12 mg/d)
- 8 mg bid at day 5
- 10 mg bid at day 6
- 12 mg bid at day 7 (for a target dosage of 24 mg/d).

Monitor patients for dose adjustments based on clinical status, concomitant use of other medications (including antipsychotics), and tolerability of up-titration.

The need to titrate iloperidone slowly to reach efficacious acute antipsychotic doses may lead to delayed effectiveness compared with antipsychotics that can be started at therapeutic doses. This problem also may be seen with up-titration of other agents with strong NE α 1 properties, including chlorpromazine, clozapine, quetiapine, and risperidone, and should be considered when treating patients who need rapid dose escalation.

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Related Resource

- Iloperidone (Fanapt) prescribing information. www.fanapt.com/fanapt-pi-may09.pdf.

Drug Brand Names

Aripiprazole • Abilify	Olanzapine • Zyprexa
Chlorpromazine • Thorazine	Paliperidone • Invega
Clozapine • Clozaril	Paroxetine • Paxil
Droperidol • Inapsine	Pimozide • Orap
Fluoxetine • Prozac	Quetiapine • Seroquel
Haloperidol • Haldol	Risperidone • Risperdal
Iloperidone • Fanapt	Thioridazine • Mellaril
Ketoconazole • Nizoral	Ziprasidone • Geodon
Methadone • Dolophine, Methadose	

Disclosures

Dr. Weiden receives research support from the National Institute of Mental Health and Ortho-McNeil Janssen. He is a consultant to AstraZeneca, Bristol-Myers Squibb/Otsuka America Pharmaceutical, Eli Lilly and Company, Forest, Ortho-McNeil Janssen, Pfizer Inc., Schering-Plough, Vanda, and Wyeth, and a speaker for Ortho-McNeil Janssen and Pfizer Inc.

Dr. Bishop receives research/grant support from the National Institute of Mental Health, NARSAD, and Ortho-McNeil Janssen.

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Clinical Point

Iloperidone needs to be titrated to a target dose of 12 to 24 mg/d over 4 to 7 days

Bottom Line

Iloperidone, a new atypical antipsychotic, may be an effective option for patients with schizophrenia who have not responded to other antipsychotics. The drug's efficacy likely is comparable to that of other antipsychotics. Its receptor binding affinity is associated with a side-effect profile that may be more tolerable for some patients compared with other antipsychotics.