Iloperidone: A Clinical Overview

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Iloperidone is a new second-generation (atypical) antipsychotic medication approved for the treatment of schizophrenia in adults. The target dose of 6 mg bid can be achieved in 4 days, with titration recommended to minimize postural hypotension. The maximum recommended dose is 12 mg bid. The tolerability profile of iloperidone is noteworthy in terms of modest weight gain, no medically important changes in lipid and glucose levels, little in the way of prolactin elevation, and absence of extrapyramidal side effects, including akathisia. However, iloperidone can prolong the QTc interval on electrocardiogram. Iloperidone may be best suited for patients who are sensitive to akathisia or who are unable to tolerate the sedation and weight gain that can occur more frequently with other antipsychotics.

(J Clin Psychiatry 2011;72[suppl 1]:19–23)

OVERVIEW OF DEVELOPMENT

Iloperidone is a second-generation (atypical) antipsychotic indicated for the acute treatment of schizophrenia in adults. Iloperidone was developed about 20 years ago by Hoechst-Roussel Pharmaceuticals and was first mentioned in a study of social behaviors in rodents published in 1993.[1] Rights to the molecule were acquired in 1997 by Titan Pharmaceuticals, who sublicensed iloperidone to Novartis for further development. As part of a global clinical development program, several registration studies were conducted, including phase 3 short- and long-term clinical trials in patients with schizophrenia.[2–4] In 2002, Novartis halted further development of iloperidone for commercial reasons. In 2004, Vanda Pharmaceuticals licensed iloperidone from Novartis, completed the clinical registration program, and obtained regulatory approval for the acute treatment of schizophrenia in adults from the US Food and Drug Administration (FDA) on May 6, 2009. Novartis Pharmaceuticals Corporation then obtained exclusive rights from Vanda to market iloperidone in the United States and Canada and also to develop a depot formulation.[5]

PHARMACOLOGIC PROFILE

Iloperidone belongs to the chemical class of piperidinyl-benzisoxazole derivatives. As with other drugs having efficacy in schizophrenia, its mechanism of action is unknown. However, as with most other second-generation antipsychotics, iloperidone is believed to exert its therapeutic effect primarily via antagonism of dopamine D_2 receptors in combination with serotonin 5-HT_{2A} antagonism.[6,7]

Pharmacokinetics

Iloperidone is well absorbed after oral administration and can be taken with or without food.[6,8,9] Time to peak concentration is 2–4 hours with single dosing and 1.5 hours with multiple dosing.[8] Iloperidone's mean elimination half-life in cytochrome P450 (CYP) 2D6 extensive metabolizers is 18 hours (23–26 hours for the metabolites), but it is substantially longer in CYP2D6 poor metabolizers (33 hours, 31–37 hours for the metabolites). Although these half-lives support once- or twice-daily dosing, the potential for orthostatic hypotension makes it prudent to titrate iloperidone using divided doses, and the product labeling recommends bid dosing. Steady-state concentrations are attained within 3–4 days. Iloperidone has an apparent clearance (clearance/bioavailability) of 47–102 L/h. Inhibitors of CYP3A4 (eg, ketoconazole, clarithromycin) or of CYP2D6 (eg, fluoxetine, paroxetine) can inhibit iloperidone elimination and result in 2-fold increases in iloperidone blood levels.[6] The product label recommends that the dosage be halved in poor metabolizers via CYP3A4 or 2D6 and in patients taking strong inhibitors of CYP2D6 and/or CYP3A4. Iloperidone is not recommended for patients with hepatic impairment.[6]

Pharmacodynamics

Iloperidone demonstrates high binding affinity for norepinephrine α_1, serotonin 5-HT_{2A}, and dopamine D_2 and D_3 receptors; moderate affinity for dopamine D_4 and serotonin 5-HT_6 and 5-HT_7 receptors; and low affinity for serotonin 5-HT_{1A}, dopamine D_1, and histamine H_1 receptors.[6] Iloperidone has no appreciable affinity for cholinergic muscarinic receptors. Functionally, iloperidone is an antagonist at the dopamine D_2 and D_3, serotonin 5-HT_{1A}, and norepinephrine α_1 and α_{2C} receptors.

EFFICACY

Short-Term Trials

The efficacy of iloperidone for acute episodes of schizophrenia was tested in 4 pivotal 4- or 6-week, randomized, double-blind, placebo- and active comparator–controlled multicenter studies. All studies enrolled adult patients 18–65 years of age. Two of these studies were accepted by the FDA as supportive of iloperidone's efficacy in the acute treatment of schizophrenia (Figure 1).[4,6,10,11]

Novartis conducted three 6-week studies.[10] In the first study, 621 patients were randomized to receive 4, 8, or

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doi:10.4088/JCP.10075su1.04

12 mg/d of iloperidone, haloperidol 15 mg/d, or placebo. When only patients with schizophrenia were included (ie, excluding patients with schizoaffective disorder), haloperidol separated statistically from placebo, but the iloperidone 8- and 12-mg/d combined group did not. Although the results suggested that the 12-mg/d dose by itself may have been therapeutic, the trial was not considered a positive trial because the outcome of the combined 8- and 12-mg/d group was the prespecified primary outcome. In the second study, 616 patients were randomized to receive 4–8 or 10–16 mg/d of iloperidone, risperidone 4–8 mg/d, or placebo. This trial was also not a positive one. When only patients with schizophrenia were included (ie, excluding patients with schizoaffective disorder), the iloperidone versus placebo comparisons were nonsignificant, while risperidone was statistically significantly superior to placebo and to iloperidone. In the third study conducted by Novartis, which was 1 of the 2 on which approval was based, 706 patients were randomized to receive 12–16 mg/d or 20–24 mg/d of iloperidone, risperidone 6–8 mg/d, or placebo. When only patients with schizophrenia were included (ie, excluding patients with schizoaffective disorder), iloperidone and the active control both produced statistically significant improvements in Brief Psychiatric Rating Scale total score compared with placebo.[6,10]

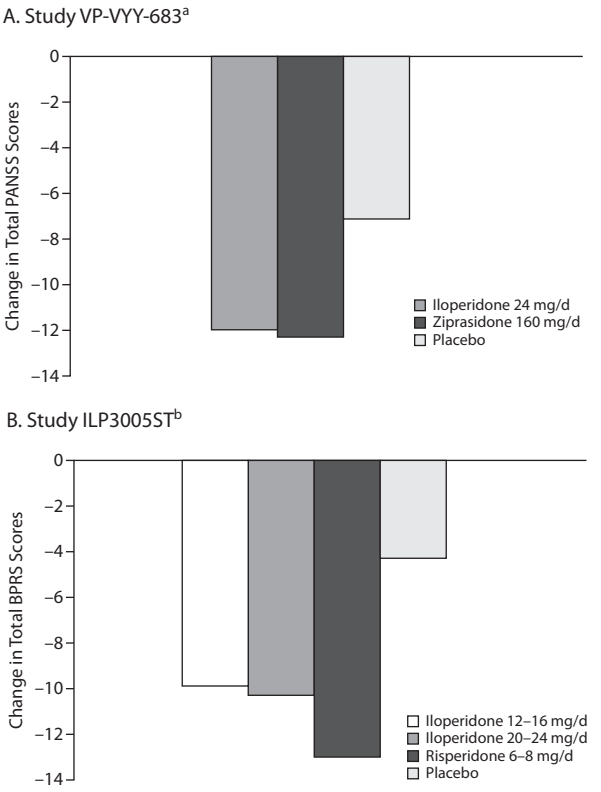
In the positive study conducted by Vanda Pharmaceuticals,[11] 606 patients were randomized to receive 4 weeks of treatment with iloperidone 24 mg/d, ziprasidone 160 mg/d, or placebo. This study found that iloperidone 24 mg/d and the active control both produced statistically significant improvements on the Positive and Negative Syndrome Scale (PANSS) scores compared with placebo.[11]

In an analysis of pooled data from all 4 trials, iloperidone demonstrated positive treatment effects across the different symptom domains of schizophrenia as represented by a PANSS 5-factor model.[12] Results of additional analyses concerning patients with schizophrenia and the combined sample of patients with either schizophrenia or schizoaffective disorder performed by the manufacturer and by the FDA can be found elsewhere.[4]

Longer Trials

Although the product labeling for iloperidone does not, at present, include information from clinical trials of maintenance treatment of schizophrenia, data are available from 3 long-term, prospective, randomized, multicenter, double-blind, flexible-dose, parallel-group trials.[13] The three 52-week studies compared the long-term efficacy and safety of iloperidone and haloperidol in patients with schizophrenia, using a non-inferiority design. Each study began with a 6-week stabilization phase, followed by a 46-week double-blind maintenance phase. Patients included in the pooled data analysis completed the initial 6-week phase with at least 20% reduction in PANSS total score at weeks 4 and 6 and a score of less than 4 on the Clinical Global Impressions of Change (CGI-C) scale. Doses could be adjusted within the range of 4–16 mg/d for iloperidone and between 5 and 20 mg/d for haloperidol.[13]

Figure 1. Study VP-VYY-683 (A) and Study ILP3005ST (B) Efficacy Outcomes (mixed model repeated measures) Supporting the Approval of Iloperidone



[a]Based on data from Cutler et al.[11] Change from baseline to endpoint in Positive and Negative Syndrome Scale (PANSS) total scores after 4 weeks. Negative numbers indicate improvement.
[b]Adapted with permission from Citrome.[4] Change from baseline to endpoint in Brief Psychiatric Rating Scale (BPRS) total scores after 6 weeks. Negative numbers indicate improvement.

Of the 1,326 patients who completed the 6-week phase, 473 (iloperidone n = 359; haloperidol n = 114) were included in the long-term efficacy analysis, and 489 (iloperidone, n = 371; haloperidol, n = 118) in the safety analysis. The primary efficacy variable was time to relapse, defined as a 25% or more increase in PANSS total score, including at least a 10-point change, discontinuation because of lack of efficacy, aggravated psychosis with hospitalization, or a 2-point increase in the 7-item CGI-C after week 6. Rates of relapse and reasons for relapse were similar between the 2 groups. Mean doses at the end of the initial 6-week phase and at the end of the long-term maintenance phase were iloperidone 11.8 and 12.5 mg/d, respectively, and haloperidol 13.2 and 12.5 mg/d, respectively. These doses are consistent with a pharmacokinetic model[8] suggesting that increasing iloperidone concentrations beyond the 5–8 ng/mL range (equivalent to about 12 mg/d) yields little additional improvement.

SAFETY AND TOLERABILITY

Overview of Adverse Effect Profile

Changes in weight. The mean change in weight from baseline to endpoint in the short-term studies was 2.0 kg in

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patients treated with iloperidone compared with −0.1 kg in those receiving placebo.[6] On the basis of data from the short-term studies, 4% of patients who received placebo and 13% of those who received iloperidone experienced weight gain of at least 7% from baseline.[6] Across all short- and long-term studies, the overall mean change in weight from baseline to endpoint was 2.1 kg.[6] During the long-term studies comparing iloperidone and haloperidol, approximately two-thirds of the total weight gain with iloperidone at endpoint occurred during the first 6 weeks of the study, with a mean additional increase in weight of 1.2 kg during the long-term phase of the study. The mean weight gain for patients who remained on iloperidone for the full 52 weeks was 4.8 kg versus 3.0 kg for haloperidol.

Extrapyramidal symptoms. Iloperidone showed no significant association with extrapyramidal symptoms (EPS), akathisia, or tremor at any dose in the clinical trials.[6]

Glucose and lipid levels. On the basis of the short-term studies, no medically important differences were observed between iloperidone and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry, including glucose, triglycerides, and total cholesterol measurements.[6] In the long-term studies of iloperidone and haloperidol, mean glucose levels increased from baseline in patients receiving iloperidone (5.90 mg/dL) versus a decrease of 0.49 mg/dL in patients randomized to haloperidol; however, increases in levels of total cholesterol and triglycerides were numerically larger in patients receiving haloperidol than in those receiving iloperidone.[13]

Increases in QTc interval. Increases in QTc interval on electrocardiogram were observed with all dose ranges of iloperidone; however, no deaths or serious arrhythmias attributable to QTc prolongation occurred in any of the clinical trials with iloperidone.[6] In an open-label QTc interval study in patients with schizophrenia or schizoaffective disorder, iloperidone 24 mg/d was associated with QTc prolongation of 9 milliseconds,[6] which is comparable to observations with ziprasidone.[14,15] Under conditions of metabolic inhibition of both CYP2D6 and CYP3A4, iloperidone 24 mg/d was associated with a mean QTc increase from baseline of about 19 milliseconds.[6] In the long-term studies, similar mean changes from baseline in QTc on electrocardiogram were observed for iloperidone and haloperidol (10.3 and 9.4 milliseconds, respectively).[13]

Orthostatic hypotension. It is recommended that iloperidone be titrated slowly from a low starting dose (1 mg bid) to a target dose of 6 mg bid over a 4-day period to avoid orthostatic hypotension due to iloperidone's α-adrenergic blocking properties.[2,6] The product labeling notes that control of symptoms may be delayed compared with some other antipsychotic drugs that do not require similar titration.[6] Decreases in supine and standing systolic and diastolic blood pressure and increases in heart rate were observed with all dose ranges of iloperidone; however, decreases in blood pressure were mostly observed within the first week of treatment and were generally not sustained.[11,16] Relatively few patients experienced orthostatic hypotension in the clinical trial program, in which the dose was increased slowly as recommended: 5% of patients receiving iloperidone 20–24 mg/d and 3% of patients receiving iloperidone 10–16 mg/d, compared with 1% of those randomized to placebo.[6] Iloperidone should be used cautiously in patients with known cardiovascular or cerebrovascular disease or who have a predisposition to hypotension.

Table 1. Spontaneously Reported Adverse Events in Short-Term Trials of Iloperidone for the Acute Treatment of Schizophrenia With Incidence ≥ 5% and 2-Fold Greater Than Placebo[a]

		Iloperidone 10–16 mg/d		Iloperidone 20–24 mg/d	
Adverse event	Placebo Rate[b]	Rate[b]	NNH[c]	Rate[b]	NNH[c]
Dizziness	7%	10%	34	20%	8
Dry mouth	1%	8%	15	10%	12
Fatigue	3%	4%	100	6%	34
Nasal congestion	2%	5%	34	8%	17
Orthostatic hypotension	1%	3%	50	5%	25
Somnolence	5%	9%	25	15%	10
Tachycardia	1%	3%	50	12%	10
Weight increase	1%	1%	ND	9%	13

[a]Adverse event rates from Fanapt prescribing information.[6]
[b]Percentage of patients reporting reaction.
[c]Number needed to harm (NNH) for iloperidone versus placebo. NNH is used to denote how many patients one would need to treat with 1 intervention versus another in order to encounter 1 additional adverse outcome.[17] The higher the NNH, the less likely that the event will be encountered with iloperidone versus the comparator, in this case placebo.
Abbreviation: ND = no difference.

Prolactin levels. Although prolactin increases were not observed in the pooled analysis of 3 of the 6-week trials, prolactin levels were not available for the iloperidone group taking 20–24 mg/d.[10] However, plasma prolactin levels in patients receiving iloperidone 24 mg/d were obtained in the Vanda Pharmaceuticals study[11] and showed a small mean increase of 2.6 ng/mL from baseline to endpoint, compared with a decrease of 6.3 ng/mL in the placebo group. In that study, elevated plasma prolactin levels were observed in 26% of adults treated with iloperidone compared with 12% of those who received placebo.[6]

Tolerability. On the basis of the pooled data from 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, there was no difference in the incidence of discontinuation due to adverse events between patients treated with iloperidone (5%) or placebo (5%). The types of adverse events that led to discontinuation were also similar for the 2 groups.

Adverse Effects in Clinical Trials

In the short-term trials of iloperidone, commonly observed (incidence ≥ 5% and 2-fold greater than placebo) adverse reactions were dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increase.[6] Dizziness, tachycardia, and weight increase were at least twice as frequent with iloperidone at a dose of 20–24 mg/d than at a dose of 10–16 mg/d. Table 1 lists rates of these adverse events and number needed to harm (NNH) for iloperidone versus placebo. In general, a single digit NNH means that the adverse reaction can be expected commonly

in day-to-day clinical practice. For example, the NNH for dizziness in the group who received iloperidone 20–24 mg/d versus placebo is 8; thus, for every 8 patients randomized to iloperidone 20–24 mg/d versus placebo, 1 additional patient with an adverse event of dizziness was recorded. In contrast, the NNH for dizziness in the group who received iloperidone 10–16 mg/d is 34, indicating that this effect is strongly dose related. Somnolence also appears to be dose related, with a NNH of 10 for iloperidone 20–24 mg/d compared with a NNH of 25 for iloperidone 10–16 mg/d. Because iloperidone does not bind appreciably to muscarinic receptors, anticholinergic adverse effects are not observed with this drug. Also, as noted above, no dose of iloperidone was significantly associated with EPS, akathisia, or tremor.

In the long-term studies that compared iloperidone with haloperidol, the most common spontaneously reported adverse events with iloperidone were insomnia and anxiety.[13]

Long-Term Health Effects

Iloperidone's product labeling contains the standard language regarding risk for tardive dyskinesia. However, iloperidone's lack of association with EPS suggests that this agent may have an advantage compared with other antipsychotics in the risk of developing tardive dyskinesia. This hypothesis remains to be tested in clinical trials designed for that purpose.

Iloperidone's weight and metabolic profile appears favorable, although weight gain of at least 7% from baseline was observed in a greater percentage of patients receiving iloperidone than placebo in the short-term trials, with the weight gain appearing to be dose related. This threshold for clinically relevant weight gain was met by 18% of subjects randomized to iloperidone 20–24 mg/d, 12% of those randomized to iloperidone 10–16 mg/d, and 4% of those receiving placebo,[6] yielding NNH values of 8 and 13, respectively.

The change in prolactin levels from baseline with iloperidone 24 mg/d in the short-term studies was small. The product labeling notes that "in the short-term trials, iloperidone was associated with modest levels of prolactin elevation compared to greater prolactin elevations observed with some other antipsychotic agents."[6] In pooled analyses from the iloperidone clinical studies, including the longer-term trials, gynecomastia was reported in 2 male subjects (0.1%) compared with 0% in patients treated with placebo, and galactorrhea was reported in 8 female subjects (0.2%) compared with 3 female subjects (0.5%) treated with placebo.[6]

CLINICAL GUIDANCE

The recommended target dose of iloperidone is 12 to 24 mg/d, administered twice daily. The dose should be titrated over 4 days to reach a dose of 12 mg/d in order to minimize dizziness and/or orthostatic hypotension (starting with 1 mg bid, then 2 mg bid, 4 mg bid, and 6 mg bid). Slower titration may be necessary for patients who are sensitive to orthostatic hypotension. Iloperidone can be administered without regard to meals. The optimal efficacious dose for iloperidone is unclear but, given dose-related tolerability concerns, a dose of 12 mg/d may be best for most patients and is consistent with a pharmacokinetic model and the long-term trials discussed above.

Iloperidone's product label notes that "in choosing among treatments, prescribers should consider the ability of iloperidone to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate iloperidone slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration."[6] The language concerning the QT interval is similar to that in the labeling for ziprasidone and would not ordinarily be an obstacle for use. The need for titration may not necessarily be an impediment for patients who are being switched from one antipsychotic to another. For those newly starting an antipsychotic, coverage with an anxiolytic may be helpful during the 4 days required to titrate to the target dose of 12 mg/d. First-episode patients, in particular, may find iloperidone easier to tolerate than some other choices because of its benign EPS profile, including the relative absence of akathisia.

No studies are currently available to inform the clinician on how best to switch to (or from) iloperidone, although 1 clinical trial is in progress (ClinicalTrials.gov identifier NCT01207414). Because of the potential for postural hypotension, concomitant use of other agents that have α_1-adrenergic antagonism should be done cautiously. Patients receiving antihypertensive medications should also be monitored carefully when starting iloperidone.

Management of potential adverse effects involves warning the patient and caregivers of the most common events and how often they can be anticipated.

Iloperidone is not recommended for patients with hepatic impairment. If patients are receiving a concomitant agent that is a CYP2D6 or 3A4 inhibitor, the dose of iloperidone should be increased if the concomitant agent is withdrawn.

CONCLUSION

Iloperidone is an antipsychotic with demonstrated efficacy for the treatment of schizophrenia in adults. Although iloperidone requires titration to a therapeutic dose, it is well tolerated with a dropout rate for adverse effects similar to that for placebo. Iloperidone's safety and tolerability profile is noteworthy for modest weight gain, no medically important changes in lipid or glucose levels, little in the way of prolactin elevation, and an absence of EPS, including akathisia. QT prolongation on electrocardiogram is similar to that reported with ziprasidone. In long-term studies, QT prolongation with iloperidone appeared similar to that observed for haloperidol. The currently available antipsychotics associated with near-zero EPS are associated with other problems of concern, such as sedation and weight gain, which can be significant obstacles to patient satisfaction and medication adherence. Iloperidone would be a reasonable choice in these situations where EPS and metabolic issues are of concern.

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Drug names: clarithromycin (Biaxin and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), iloperidone (Fanapt), ketoconazole (Nizoral and others), paroxetine (Paxil, Pexeva, and others), risperidone (Risperdal and others), ziprasidone (Geodon).
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Potential conflicts of interest: In the past 12 months, **Dr Citrome** has been a consultant or on the speakers or advisory boards for, has received honoraria from, has a small number of shares in, or conducted clinical research supported by the following: Alexza, Alkermes, AstraZeneca, Avanir, Bristol-Myers Squibb, Eli Lilly, Janssen, Johnson & Johnson, Lundbeck, Merck, Novartis, Noven, Pfizer, Shire, Sunovion, and Valeant.
Funding/support: The author acknowledges Ruth Ross, MA, Project Manager, Healthcare Global Village, for editorial assistance in developing the manuscript. The preparation and dissemination of this article and supplement were supported by an educational grant from Sunovion Pharmaceuticals Inc.

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