20 ILOPERIDONE: PLACEBO- AND ZIPRASIDONE-CONTROLLED STUDY IN PATIENTS WITH SCHIZOPHRENIA

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Abstract

Background: Iloperidone is a novel atypical antipsychotic being developed for the treatment of schizophrenia. Previous clinical trials assessing the efficacy of iloperidone have used haloperidol and risperidone as active comparators. However, these comparators have shorter titration schedules and recognizably different safety and tolerability profiles than iloperidone, introducing potential bias in efficacy assessments. Ziprasidone was chosen as the active comparator in this international randomized, double-blind, placebo-controlled study of iloperidone because of its similar titration schedule and safety and tolerability profile.

Methods: Doses were titrated on a fixed schedule (days 1–7) to reach fixed maintenance (days 8–28) of iloperidone 24 mg/d (12 mg bid; ILO), ziprasidone 160 mg/d (80 mg bid; ZIP), or placebo (PLA). Primary efficacy variable was change from baseline to end point (day 28) in Positive and Negative Syndrome Scale total score (PANSS-T) for ILO compared with PLA based on a mixed-effects model repeated measures analysis. Safety and tolerability assessments included adverse events (AEs); extrapyramidal symptoms (EPS) and akathisia using the Extrapyramidal Symptoms Rating Scale (ESRS) and Barnes Akathisia Scale (BAS); vital signs; laboratory values; and electrocardiography.

Results: Of the 593 randomized patients, 65% of ILO, 66% of ZIP, and 60% of PLA patients completed the study. From baseline to end point, the ILO group showed significantly greater improvement than the PLA group in PANSS-T (−12.0, $P<.01$), as did the ZIP group (−12.3, $P<.05$). Significant improvements from baseline to end point were observed for ILO compared with PLA in PANSS-derived Brief Psychiatric Rating Scale (BPRS; −7.4, $P<.05$) and subscale scores PANSS positive syndrome (PANSS-P; −4.2, $P<.001$) and PANSS negative syndrome (PANSS-N; −3.0, $P<.05$). ZIP showed significantly greater improvements than PLA in BPRS (−7.2, $P<.05$), PANSS-P (−4.2, $P<.01$), and PANSS-N (−3.1, $P<.05$). All treatments were generally well tolerated. Commonly reported AEs for ILO were dizziness, sedation, weight increase, and dry mouth, and for ZIP were sedation, dizziness, EPS, and akathisia. The following ESRS subscales significantly improved from baseline to end point for ILO vs PLA ($P<.05$): Clinical Global Impression of Severity (CGI-S) of dystonia, acute torsion dystonia, dyskinesia physician total, trunk/limb dyskinesia, CGI-S of akathisia, and akathisia. On the BAS at end point compared with PLA, ZIP showed significant worsening ($P<.05$), whereas ILO was similar. Mean changes from baseline to end point (+2.6, +1.9, and −6.3 ng/mL) for prolactin were different among the ILO, ZIP, and PLA groups, respectively. For ILO, mean weight increased from 82.8 kg at baseline to 85.4 kg at day 14 and then stabilized to 85.6 kg at end point. At end point, mean weight increases from baseline for ILO, ZIP, and PLA were 2.8, 1.1, and 0.5 kg, respectively. The following mean changes (mg/dL) from baseline to end point were observed for glucose (ILO +7.9; ZIP +4.7; PLA +3.2), total cholesterol (ILO +8.1; ZIP +4.1; PLA −0.5), and triglycerides (ILO +0.8; ZIP +4.6; PLA +19.5).

Conclusion: Iloperidone, administered twice daily at a dose of 24 mg/d, is an effective treatment for patients with schizophrenia. With its favorable safety and tolerability profile, iloperidone may offer an alternative treatment option to existing antipsychotics for patients with schizophrenia.

Background

- The CATIE study showed that currently available antipsychotic drugs, while demonstrating improvements over earlier medications, are associated with poor adherence, treatment discontinuation, and frequent switching attributable to lack of efficacy and intolerability in patients with chronic schizophrenia.[1]
- Iloperidone is a novel antipsychotic and mixed D_2/5-HT_2 antagonist.[2-4]
  - Low affinity for histamine H_1 receptors may lower risk of weight gain and somnolence.[3,4]
  - High affinity for α_{2C}-adrenergic receptors may provide antidepressant and anxiolytic activity and improved cognitive function, but may also be associated with orthostatic hypotension.[2,3]
- In previous trials, iloperidone showed good tolerability with low weight gain, low incidence of extrapyramidal symptoms, and mild effects on prolactin and metabolic parameters.

Objectives

- Primary: evaluate the efficacy of iloperidone 24 mg/d vs placebo in a 4-week trial in hospitalized patients with acute psychotic exacerbation of schizophrenia
- Secondary: characterize the efficacy, safety, and tolerability of iloperidone 24 mg/d and an active control (ziprasidone) individually vs placebo

Methods

- Four-week, prospective, randomized, double-blind study conducted from November 2005 to September 2006 at 35 centers in the US and 9 in India
- Dose titration and maintenance periods in inpatient setting
- Dose titration phase (days 1–7) with ascending doses: iloperidone (1–12 mg bid), ziprasidone (20–80 mg bid)
- Maintenance phase (days 8–28) with stable dosing: iloperidone 12 mg bid, ziprasidone 80 mg bid
- Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression of Severity (CGI-S), Extrapyramidal Symptoms Rating Scale (ESRS), and Barnes Akathisia Scale (BAS) administered at baseline (day 0) and on days 7, 14, 21, and 28. In addition, PANSS was administered on Day 10.

Main Inclusion Criteria

- Men and women aged 18–65 years meeting DSM-IV criteria for schizophrenia
- Baseline PANSS-Total (-T) score ≥70; PANSS-Positive (-P) score ≥4 in ≥2 of the following: delusions, conceptual disorganization, hallucinations, and suspiciousness/persecution; CGI-S ≥4.

Main Exclusion Criteria

- DSM-IV diagnosis of schizophreniform or schizoaffective disorder, or other primary Axis I psychiatric disorder
- Diagnosis or history of chemical dependence in the preceding 6 months
- Failure of 2 courses of antipsychotics within previous 2 years or hospitalization for >14 days immediately prior to screening
- Prolonged QT syndrome or clinically significant gastrointestinal, hepatic, or renal disease

Statistical Analysis

- Efficacy analysis included a modified intent-to-treat (ITT) population
  - Patients who received ≥1 treatment dose and underwent baseline and ≥1 postbaseline PANSS evaluation
- Primary efficacy outcome: mean change from baseline to last observation in PANSS-T score, analyzed using mixed-effects model repeated measures (MMRM)
- Change from baseline, using analysis of covariance (ANCOVA), and categorical outcomes, using the Cochran-Mantel-Haenszel test
- Significance tests 2-tailed when appropriate ($P\leq .05$)

Results

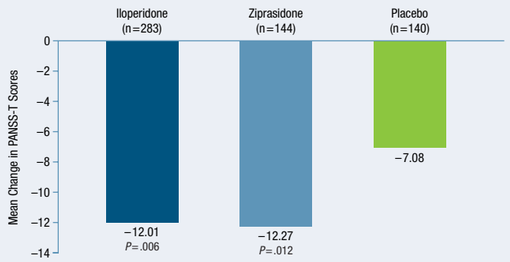
Patient Disposition

- 913 patients screened; 593 randomized (iloperidone, n=295; ziprasidone, n=149; placebo, n=149)
- Similar completion rates: iloperidone (65%), ziprasidone (66%), placebo (60%)
- Withdrawn consent most frequent reason for early discontinuation, followed by unsatisfactory therapeutic effect and adverse events (AEs)

Table 1. Baseline Characteristics

Characteristic	Iloperidone (n=295)	Ziprasidone (n=149)	Placebo (n=149)	Total (N=593)
Mean age, y (SD)	39.5 (10.4)	40.0 (9.9)	40.7 (10.4)	39.9 (10.3)
Men, n (%)	245 (83.1)	113 (75.8)	114 (76.5)	472 (79.6)
Ethnicity, n (%)				
White	111 (37.6)	51 (34.2)	46 (30.9)	208 (35.1)
Black	147 (49.8)	76 (51.0)	76 (51.0)	299 (50.4)
Asian	25 (8.5)	12 (8.1)	15 (10.1)	52 (8.8)
Mean weight, kg (SD)	82.2 (17.4)	80.5 (17.1)	81.1 (18.7)	81.5 (17.6)
Mean height, cm (SD)	173.8 (9.2)	172.7 (10.1)	172.0 (10.5)	173.1 (9.8)
DSM-IV classification, n (%)				
Disorganized	13 (4.4)	3 (2.0)	7 (4.7)	23 (3.9)
Paranoid	246 (83.4)	127 (85.2)	128 (85.9)	501 (84.5)
Undifferentiated	36 (12.2)	19 (12.8)	14 (9.4)	69 (11.6)

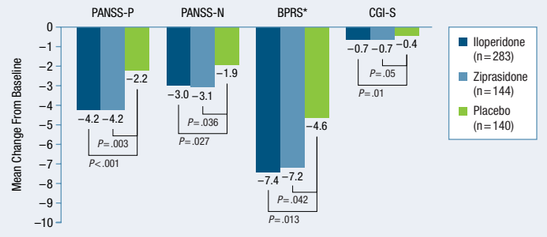
Figure 1. Mean Change From Baseline in PANSS-T Scores at Day 28



All P values vs placebo. Negative change indicates improvement.

- Significantly greater reduction from baseline in PANSS-T scores was observed with iloperidone (−12.0, $P<.01$) and ziprasidone (−12.3, $P<.05$) when compared with placebo (−7.1).
- Similar significant results were observed using the last-observation-carried-forward (LOCF) model.

Figure 2. Mean Changes From Baseline in PANSS-P, PANSS-N, BPRS, and CGI-S Scores at Day 28



*BPRS Total score derived from PANSS

- Many patients received a concomitant medication during the study (91–94%).
- Most commonly initiated were benzodiazepines (81–86%).
  - Benzodiazepine derivatives (eg, lorazepam): iloperidone 81.7%, ziprasidone 85.9%
  - Benzodiazepine-related drugs (eg, zolpidem): iloperidone 61.7%, ziprasidone 65.1%

Table 2. Most Frequent Treatment-Emergent Adverse Events

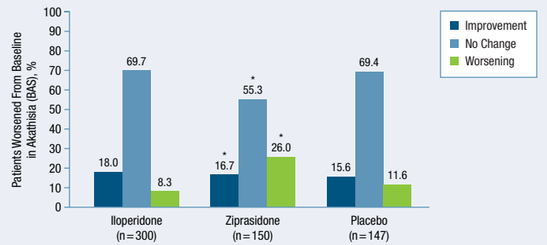
Adverse Event,* n (%)	Iloperidone (n=300)	Ziprasidone (n=150)	Placebo (n=147)
At least 1 AE	255 (85)	130 (87)	108 (74)
Dizziness	51 (17)	20 (13)	11 (8)
Sedation	38 (13)	41 (27)	12 (8)
Weight increased	34 (11)	7 (5)	3 (2)
Dry mouth	26 (9)	11 (7)	1 (0.7)
Heart rate increased	24 (8)	9 (6)	1 (0.7)
Nasal congestion	25 (8)	5 (3)	4 (3)
Tachycardia	28 (9)	3 (2)	1 (0.7)
EPS	10 (3)	14 (9)	3 (2)
Agitation	10 (3)	10 (7)	4 (3)
Orthostatic hypotension	21 (7)	0	3 (2)
Somnolence	12 (4)	9 (6)	2 (1)
Restlessness	11 (4)	8 (5)	3 (2)
Anxiety	9 (3)	8 (5)	1 (0.7)
Akathisia	4 (1)	11 (7)	0

*AE reported by the investigator that occurred in ≥5% of iloperidone or ziprasidone patients, and at least twice the rate of placebo. No statistical analyses were performed.

- No serious AEs were considered related to iloperidone or ziprasidone.
- Treatment-emergent AEs resulted in discontinuation for 5% of iloperidone, 8% of ziprasidone, and 8% of placebo patients.
- No deaths occurred during the double-blind phase.

Akathisia and Extrapyramidal Symptoms (EPS)

Figure 3. Change in Barnes Akathisia Scale at End Point



*Significant worsening vs placebo ($P<.05$)

- Iloperidone was similar to placebo on BAS at each data point and at end point.
- Patients treated with ziprasidone experienced worsening from baseline; statistically significant worsening was observed from day 14 through end point.
- ESRS scores were similar between iloperidone and placebo.
- Ziprasidone showed significant worsening from baseline in ESRS scores compared with placebo ($P<.05$).

Vital Signs

- Incidence of orthostatic response (defined as 30 mm Hg fall in systolic blood pressure) in the iloperidone, ziprasidone, and placebo groups was 13%, 2%, and 6%, respectively.
- No cases of sustained orthostasis (defined as an orthostatic response on both day 14 and at end point) occurred in any group.

QT Interval

Table 3. Mean Changes in QT Corrected for Heart Rate (QTc) Interval Using Fridericia Correction

Time Point	Iloperidone (n=300)	Ziprasidone (n=150)	*P* Value*
14 Days	11.4 msec	11.3 msec	<.001
28 Days	7.2 msec	6.1 msec	<.001

**P* values are versus placebo.

- Two iloperidone patients and one ziprasidone patient experienced ≥15% increases in QTc interval.
- No patient had a change in QTc interval from <500 msec at baseline to ≥500 msec.

Weight and Metabolic Parameters

- From baseline to end point, mean weight increased 2.8 kg in the iloperidone group, 1.1 kg in the ziprasidone group, and 0.05 kg in the placebo group.
- Mean changes in laboratory values from baseline to end point were similar across treatment groups, varying little over time for most parameters. Parameters of note were glucose, total cholesterol, triglycerides, and prolactin.

Table 4. Laboratory Value Changes From Baseline at Day 28

Parameter, Mean Change (SD)	Iloperidone (n=300)	Ziprasidone (n=150)	Placebo (n=147)
Glucose (mg/dL)	7.9 (28.7)	4.7 (28.3)	3.2 (22.4)
Total cholesterol (mg/dL)	8.1 (31.8)	4.1 (34.2)	−0.5 (35.5)
Triglycerides (mg/dL)	0.8 (88.6)	4.6 (101.9)	19.5 (110.3)
Prolactin (ng/mL)	2.6 (26.7)	1.9 (26.0)	−6.3 (22.4)

No statistical analyses were performed.

Conclusions

- Iloperidone 24 mg/d for 4 weeks was efficacious in treating schizophrenia, with a treatment response similar to that of ziprasidone.
- Compared with ziprasidone, iloperidone was associated with lower rates of many AEs that are particularly troublesome with antipsychotics, including sedation, somnolence, EPS, akathisia, agitation, and restlessness; iloperidone was also associated with higher rates of weight gain, tachycardia, orthostatic hypotension, and dizziness as reported as an AE. Most AEs were mild to moderate.
- Iloperidone was associated with less EPS and akathisia than ziprasidone as measured by ESRS and BAS.
- Changes in QT interval were similar with iloperidone and ziprasidone; no patient had a change in QTc interval from <500 msec at baseline to ≥500 msec.
- Weight gain and mean changes in prolactin, total cholesterol, triglycerides, and glucose were similarly low in the iloperidone and ziprasidone groups. Weight gain was slightly higher with iloperidone, but triglycerides increased less with iloperidone than with either ziprasidone or placebo.
- With its favorable safety and tolerability profile, iloperidone may offer an alternative treatment option for patients with schizophrenia.

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