Iloperidone (Fanapt®)

INTRODUCTION

Antipsychotics are considered the mainstay of therapy for patients with schizophrenia. With the advent of new second-generation or atypical antipsychotics the safety of therapy has evolved. Atypical antipsychotics are considered to have similar efficacy to older first-generation agents but with a lower risk of extrapyramidal symptoms (EPS) and tardive dyskinesia. These agents although more tolerable, are associated with their own array of adverse events (i.e. metabolic disturbances).

Despite the improved tolerability profile, >50% of patients on an atypical antipsychotic will discontinue therapy within 6 months. Poor adherence is attributed to lack of efficacy and poor tolerability. The need for effective and well tolerated treatment has prompted researchers to develop more agents. One such agent is iloperidone.

INDICATION

Iloperidone is approved for the acute treatment of schizophrenia in adults. Current labeling does not recommend iloperidone as first line treatment.

PHARMACOLOGY

Figure 1. Structure of Iloperidone

Figure 2. Structure of risperidone
Iloperidone is a piperidinyl-benzisoxazole derivative with mixed D₂/5-HT₂ receptor antagonism with high affinity for 5-HT₂A, α₁-adrenergic, α₂C-adrenergic D₂, and D₃ receptors; moderate affinity for D₄, 5-HT₆ and 5-HT₇ receptors; and low affinity for 5-HT₁A, 5-HT₂C, D₁ and H₁ receptors. It was synthesized with the intention to develop an atypical antipsychotic with a low potential for EPS.

Affinity for the 5-HT₂C receptors may enhance iloperidone's efficacy in treating the negative symptoms of schizophrenia and provide some anxiolytic activity. Binding at the α₂C-adrenergic receptors (increasing postsynaptic dopamine and norepinephrine concentrations) and the 5-HT₁A receptors (increasing extracellular glutamate) may improve attention and cognitive function in patients with schizophrenia.

**PHARMACOKINETICS**

Absorption: Iloperidone is well absorbed with an absolute bioavailability of 96%. Peak plasma concentrations occur 2 to 4 hours after a dose. Administration with a standard high-fat meal may delay the rate of absorption by ~ 1 hour; however, it does not have a significant effect on AUC or Cmax. Steady-state concentrations are reached within 3 to 4 days.

Distribution: Iloperidone and its metabolites are approximately 95% bound to serum proteins at therapeutic concentrations. The apparent volume of distribution is between 1340-2800 L.

Metabolism: Iloperidone is extensively metabolized in the liver via carbonyl reduction, hydroxylation (mediated through CYP2D6) and O-demethylation (mediated through CYP3A4). Iloperidone has two active metabolites, P95 and P88. P95 represents 47.9% of the AUC of iloperidone in extensive metabolizers (EM) and 25% in poor metabolizers (PM). P88 accounts for 19.5% and 34% of total plasma exposure in EM and PM, respectively.

Elimination: Following oral administration the elimination half-life of iloperidone ranges between 18 and 33 hours, depending on whether the patient is an EM or PM. For the active metabolites P95 and P88, the elimination half-lives for EM are 23 and 26 hours, respectively; and for PM are 31 and 37 hours, respectively. Less than 1% of the dose is excreted unchanged. The majority is excreted in the urine (mean 58.2% and 45.1% in EM and PM, respectively), with the remaining in the feces.

**DOSAGE AND ADMINISTRATION**

The recommended starting dose of iloperidone is 1 mg twice daily, slowly titrated to a target dose of 6 to 12 mg twice daily. The slow titration schedule consists of daily dosage adjustments to 2 mg twice daily, 4 mg twice daily, 6 mg twice daily, 8 mg twice daily, 10 mg twice daily and 12 mg twice daily on days 2, 3, 4, 5, 6 and 7, respectively. This schedule is recommended to avoid severe orthostatic hypotension. Of note, due to
the slow titration schedule, control of symptoms may be delayed during the first week of therapy. The maximum recommended dose is 24 mg/day. Iloperidone can be taken without regard to meals.

Iloperidone tablets are available in the following strengths: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg. There is a titration pack available that will provide patients with the first 4 days of therapy.

**CONTRAINDICATIONS**

Iloperidone is contraindicated in patients with known hypersensitivity to the agent or any component of the formulation.

**WARNINGS AND PRECAUTIONS**

Elderly patients with dementia-related psychosis are at a higher risk of cerebrovascular adverse events (i.e. stroke, TIA) and death when treated with atypical antipsychotic drugs. Iloperidone is not approved for treatment of dementia-related psychosis.

**QTc prolongation**

In an open-label QTc study in patients with schizophrenia or schizoaffective disorder (n=160), FANAPT was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily. The effect of FANAPT on the QT interval was augmented by the presence of CYP450 2D6 or 3A4 metabolic inhibition (paroxetine 20 mg once daily and ketoconazole 200 mg twice daily, respectively). Under conditions of metabolic inhibition for both 2D6 and 3A4, FANAPT 12 mg twice daily was associated with a mean QTcF increase from baseline of about 19 msec (FANAPT™ Prescribing Information).

No cases of torsade de pointes (TDP) or other severe cardiac arrhythmias have been observed with iloperidone; however, TDP has occurred with some other antipsychotics. Therefore, iloperidone should be avoided in patients with a history of significant cardiac disease (i.e. acute myocardial infarction), cardiac conduction defects (i.e. AV block, bundle-branch block, cardiac arrhythmias), QT prolongation, uncompensated heart failure, or electrolyte imbalances (i.e. hypokalemia, hypomagnesemia) since these conditions may increase the risk of drug-induced QT prolongation. The drug should be discontinued in any patient with persistent QTc measurements greater than 500 msec. A baseline EKG is recommended; however, there are no specific monitoring parameters identified by the manufacturer (FANAPT™ Prescribing Information).

There may be possible potentiation of QTc prolongation when iloperidone is administered with Class 1A (i.e. quinidine, procainamide) or Class III (i.e. amiodarone, sotalol) antiarrhythmics, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (i.e., gatifloxacin, moxifloxacin) or other classes of medication known to prolong the QTc interval (i.e. pentamidine, levomethadyl acetate, methadone).
FANAPT should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. (FANAPT™ Prescribing Information)

Caution is warranted when prescribing FANAPT with drugs that inhibit FANAPT metabolism and in patients with reduced activity of CYP2D6. It is recommended that patients being considered for FANAPT treatment who are at risk for significant electrolyte disturbances have baseline serum potassium and magnesium measurements with periodic monitoring. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. (FANAPT™ Prescribing Information)

If patients taking FANAPT experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring (FANAPT™ Prescribing Information).

Iloperidone may cause extrapyramidal symptoms and tardive dyskinesia which may be irreversible. In short-term clinical trials the rates of EPS ranged between 4.0 and 5.4%. However, in a 52-week long-term trial the incidence of EPS was considerably lower at 0.8%. Iloperidone may also cause neuroleptic malignant syndrome (NMS).

Iloperidone should be used with caution in patients with hematological disease. Hematologic effects including leukopenia, neutropenia and agranulocytosis have been associated with antipsychotic use. Routine monitoring is recommended during the first few months of therapy. The drug should be discontinued if a clinically significant decline in the WBC count occurs.

In clinical trials, iloperidone was associated with seizures in a small number of patients (0.1%). Although the incidence was not higher than placebo (0.3%), patients with a seizure disorder should be treated cautiously with iloperidone since lowering of seizure threshold is thought to be a class effect.

Iloperidone has a high affinity for α₁-adrenergic receptors leading to vasodilation and possibly orthostatic hypotension. During initial dose titration orthostatic hypotension may occur; however, sustained orthostatic hypotension is fairly uncommon (< 5%). Adherence to the recommended titration schedule and possibly administration with food will help prevent/reduce this effect.

Iloperidone is classified as FDA pregnancy category C. Breast-feeding should be avoided during iloperidone administration. Women that were breast-feeding were excluded from clinical trials and it is not known if iloperidone is excreted in human breast milk.

Iloperidone can cause hyperprolactinemia, likely due to central D₂ antagonism. Elevations in prolactin may result in infertility, or other endocrine abnormalities. Close monitoring for adverse endocrine effects is advisable during the use of iloperidone.
Iloperidone may cause sedation and/or CNS depression that may interfere with cognitive and motor functioning. The sedative effects may be more common after initiation and during the titration phase. Patients should be advised to refrain from driving or operating equipment until they know how the drug will affect them.

**CLINICAL TRIALS**

Iloperidone which received FDA approval in May 2009 has been evaluated in seven phase III clinical trials.

Potkin et al. 2008

The efficacy of iloperidone was examined in a pooled analysis (n = 1943) of three 6-week, prospective, randomized, placebo- and active-controlled trials. In Study One, patients were randomized to receive iloperidone 4 mg/d (n = 121), 8 mg/d (n = 125), or 12 mg/d (n = 124), haloperidol 15 mg/d (n = 124), or placebo (n = 127). In Study Two, patients received iloperidone 4 to 8 mg/d (n = 153) or 10 to 16 mg/d (n = 154), risperidone 4 to 8 mg/d (n = 153), or placebo (n = 156). In Study Three, patients received iloperidone 12 to 16 mg/d (n = 244) or 20 to 24 mg/d (n = 145), risperidone 6 to 8 mg/d (n = 157) or placebo (n = 160). The trials included patients aged 18-65 years with an acute or sub-acute exacerbation of schizophrenia and a PANSS-T score of ≥ 60 (mean baseline score of ~95). In Study One, the primary efficacy variable was change from baseline to end point in PANSS-T scores; in Studies Two and Three, the primary efficacy variable was change in the Positive and Negative Syndrome Scale-derived Brief Psychiatric Rating Scale scores. Analysis of covariance using last observation carried forward in the intent-to-treat population was used to analyze results. At least one iloperidone dosing group in each study demonstrated significantly better efficacy than placebo. (Study One, iloperidone 12 mg/d [P = 0.047]; Study 2, 4-8 mg/d [P = 0.012] and 10-16 mg/d [ P = 0.001]; and Study Three, 20-24 mg/d [ P = 0.010]). Active controls were also significantly more effective than placebo.

Since the iloperidone titration schedule used in the above studies required two weeks to reach therapeutic steady-state levels, an additional analysis was also performed that took into account the duration of treatment. The post-hoc analysis only included subjects who received active treatment for at least two weeks (n= 1553). This analysis was conducted to eliminate the impact of early discontinuations and to evaluate patients who had reached steady-state therapeutic doses of iloperidone for at least one week of treatment. This pooled analysis demonstrated a significant reduction in the Positive and Negative Syndrome Scale-Total (PANSS-T) score for iloperidone 4-8 mg/d (-11.6; p < 0.01), iloperidone 10-16 mg/d (-14.1; p < 0.001) and iloperidone 20-24 mg/d (-16.5; p < 0.001) as compared to placebo (-7.7) [Table 2, S8]. Although no statistical analysis was performed, the post-hoc analysis indicated comparable reductions in PANSS-T scores for patients receiving iloperidone 20 to 24 mg/d versus those receiving haloperidol 15 mg/d or risperidone 4-8 mg/d (-16.5, -18.8, -18.9, respectively, Table 2).
Overall, researchers concluded that iloperidone is effective for the treatment of patients with schizophrenia or schizoaffective disorder and may provide a beneficial treatment option.

Weiden et al. 2008

Weiden et al. assessed the short-term (six week) safety of iloperidone in the three trials analyzed by Potkin et al.; the pooled safety analysis consisted of 1912 patients who were treated with at least one dose of study medication. They concluded that iloperidone is fairly well tolerated with the most common treatment-associated adverse events being dizziness, headache, dry mouth, nausea, and insomnia. Dose dependent adverse reactions include abdominal discomfort, dizziness, hypotension, tachycardia and weight increase. (See Table 1 and 2.) Discontinuation due to adverse events was 4.8% for iloperidone, 7.6% for haloperidol, 6.2% for risperidone, and 4.8% for placebo. Compared to the risperidone and haloperidol groups, the iloperidone cohorts performed better on the Extrapyramidal Symptom Rating Scale (ESRS) and Barnes Akathisia Scale (BAS). With regard to the overall EPS rating (ESRS), there was a significant improvement from baseline to end point with all of the iloperidone doses (all P < 0.05). An analysis of results from the four subscales of the BAS showed that the akathisia profile of patients on all doses of iloperidone was comparable to that of patients on placebo. Prolactin levels decreased with iloperidone; they increased significantly with risperidone and haloperidol.

In general, the increases in weight observed with iloperidone were modest and similar to those observed with risperidone. In the last observation carried forward analysis, patients taking iloperidone at all doses gained slightly more weight than those taking placebo (1.5 kg, 2.1 kg, and 1.7 kg with 4-8 mg/d, 10/16 mg/d, and 20-24 mg/d; all P < 0.05). Study subjects who took risperidone also gained significantly more weight than those taking placebo (1.5 kg vs -0.3 kg, P < 0.05). Patients taking haloperidol lost 0.1 kg. In patients who completed the studies, (iloperidone 4-8 mg, n = 162; 10-16 mg, n = 239, 20-24 mg, n = 79; haloperidol, n = 41; risperidone, n = 176; placebo, n = 162), average weight gain was 2.4 kg in each iloperidone dosing group, 0.9 kg in the haloperidol group, and 1.8 kg in the risperidone group. Completer patients taking placebo lost 0.4 kg.

Iloperidone was associated with no change from baseline in total cholesterol, mild elevation in serum glucose, and slight decrease in triglycerides (all labs non-fasting). With regard to systolic blood pressure, iloperidone decreased readings as follows: supine (-1.3, -1.6, -3.0 mm Hg) and standing (-4.8, -4.7, -7.3 mm Hg) for the 4.8 mg/d, 10-16 mg/d, and 20 to 24 mg/d dosages, respectively (all P < 0.05 vs placebo). With regard to diastolic blood pressure, decreases in supine (-1.9, -0.7, -1.0 mm Hg) and standing (-4.4, -4.5, -4.8 mm Hg), respectively, were observed with the 4 to 8 mg/d, 10 to 16 mg/d, and 20 to 24 mg/d dosages (all P < 0.05 vs placebo). Blood pressure decreases were primarily observed within the first week of treatment and, in general, were not sustained. No significant changes in blood pressure were noted for haloperidol, risperidone, or placebo.
The QTc interval increased significantly in all iloperidone dosing groups--the least squares mean change from baseline to end point ranged from 2.9-9.1 msec (2.9 msec in the 4 to 8 mg/d, 3.9 msec in the 10 to 16 mg/d, 9.1 msec in the 20 to 24 mg/d, all P < 0.05). The average increase in the haloperidol cohort was 5.0 msec (P < 0.05). There were no significant QTc changes in the risperidone (LS mean increase = 0.6 msec) or placebo (no mean change) groups. There were no deaths or serious arrhythmias attributable to QT prolongation.

Adverse event results (labs, vital signs, physical exam, EKG) are least squares (LS) mean values from baseline to end point.(p. S13).
Table 1. Treatment-Related Adverse Events Occurring in ≥ 5% of Patients (Weiden)

<table>
<thead>
<tr>
<th>Event (%)</th>
<th>ILO 4-8 mg/d (n=463)</th>
<th>ILO 10-16 mg/d (n=456)</th>
<th>ILO 20-24 mg/d (n=125)</th>
<th>HAL 15mg/d (n=118)</th>
<th>RIS 4-8 mg/d (n=306)</th>
<th>Placebo (n=440)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>3.7</td>
<td>1.5</td>
<td>4.8</td>
<td>13.6</td>
<td>6.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12.1</td>
<td>10.3</td>
<td>23.2</td>
<td>5.1</td>
<td>7.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5.2</td>
<td>7.9</td>
<td>10.4</td>
<td>2.5</td>
<td>2.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7.8</td>
<td>5.5</td>
<td>4.8</td>
<td>11.0</td>
<td>5.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0.9</td>
<td>0.9</td>
<td>0.8</td>
<td>11.9</td>
<td>2.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Extrapyramidal disorder</td>
<td>5.4</td>
<td>4.8</td>
<td>4.0</td>
<td>20.3</td>
<td>9.5</td>
<td>4.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4.3</td>
<td>4.6</td>
<td>6.4</td>
<td>7.6</td>
<td>1.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>4.8</td>
<td>5.0</td>
<td>5.6</td>
<td>1.7</td>
<td>2.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5.0</td>
<td>5.7</td>
<td>8.0</td>
<td>6.8</td>
<td>5.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Tremor</td>
<td>2.8</td>
<td>2.6</td>
<td>4.8</td>
<td>22.0</td>
<td>6.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Sustained orthostatic hypotension</td>
<td>0.4</td>
<td>3.8</td>
<td>4.8</td>
<td>0.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clinically significant increase in weight (&gt;7%)</td>
<td>10.9</td>
<td>12.8</td>
<td>15.2</td>
<td>5.1</td>
<td>11.9</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Table 2. Mean Change in Metabolic Parameters (Weiden)

<table>
<thead>
<tr>
<th>Parameter (95%CI)</th>
<th>ILO 4-8 mg/d (n=463)</th>
<th>ILO 10-16 mg/d (n=456)</th>
<th>ILO 20-24 mg/d (n=125)</th>
<th>HAL 15mg/d (n=118)</th>
<th>RIS 4-8 mg/d (n=306)</th>
<th>Placebo (n=440)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mg/dl</td>
<td>7.2*</td>
<td>9.0 *</td>
<td>16.2*</td>
<td>10.8*</td>
<td>3.6</td>
<td>-3.6</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>0 *</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-3.9</td>
<td>-7.7</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>-26.5 *</td>
<td>-26.5</td>
<td>-26.5</td>
<td>0*</td>
<td>-26/5</td>
<td>-35.4</td>
</tr>
<tr>
<td>Prolactin, ug/l</td>
<td>-38.0</td>
<td>-23.1</td>
<td>NA</td>
<td>115.8*</td>
<td>214.5*</td>
<td>-57.4</td>
</tr>
</tbody>
</table>

* Indicates significant difference vs. placebo (p< 0.05)

Cutler et al. 2008

Another phase III trial was conducted to address some of the limitations (i.e. possible bias) of the first three trials. Cutler et al compared iloperidone to ziprasidone and placebo in a four-week, double-blind, multicenter trial in 593 patients with schizophrenia and a baseline PANSS-T score > 70. Ziprasidone was included as an active control to
validate the iloperidone cohort’s response to treatment. Patients were randomized to receive iloperidone 24mg/d, ziprasidone 160 mg/d or placebo. All agents were administered twice daily with food and titrated over a seven day period to the specified dose; subjects were then treated for three weeks (maintenance period). The primary efficacy end point was change from baseline in PANSS-T (mixed-effects model repeated measures analysis). Safety end points included adverse events, EPS and akathisia.

Baseline characteristics were similar between groups with a mean age of 40 years. At 4 weeks 65% (193/593) receiving iloperidone, 66% (98/593) receiving ziprasidone and 60% (90/593) receiving placebo completed the study. There was significantly greater improvement in the PANSS-T scores for both iloperidone and ziprasidone vs. placebo (-12.0, -12.3 vs. -7.1; p<0.01 and p<0.05, respectively).

The most common adverse events with iloperidone as compared to placebo were dizziness (17% vs. 8%), sedation (13% vs. 8%), weight gain (11% vs. 2%), HR increase (8% vs. 0.7%) and orthostatic hypotension (7% vs. 2%). Discontinuation rates due to adverse events were similar for iloperidone, ziprasidone and placebo; 5%, 8% and 8%, respectively. Iloperidone did not result in significant worsening of EPS or akathisia. Compared to placebo, ziprasidone was associated with significant worsening of the CGI-S of the parkinsonism and akathisia subscales (P < 0.05).

From baseline to day 14, mean change in the QTcF was 11.4 msec and 11.3 msec for iloperidone and ziprasidone, respectively (P < 0.001 vs placebo). At endpoint, the QTcF interval prolongations decreased to 7.2 and 6.1 msec for iloperidone and ziprasidone, respectively (p<0.001 vs. placebo). The average maximum change (prolongation) in QTc interval was 16.2 msec for iloperidone and 12.3 msec for ziprasidone; both of these were significantly greater than the change with placebo, -2.4 msec; (P < 0.001 for both). No study patient experienced a change in QTc interval from less than 500 msec to greater than 500 msec.

Per Cutler et al., a clinically meaningful orthostatic change is a 30 mm-Hg decrease in systolic blood pressure; sustained orthostasis is the presence of an orthostatic response on day 14 and at end point. An orthostatic response occurred in 13% patients treated with iloperidone, 2% of patients treated with ziprasidone, and 6% of patients treated with placebo. Among the patients treated with iloperidone, there were 39 episodes of orthostasis; 24 (62%) of these happened during the first week. No patient experienced sustained orthostasis.

The mean change from baseline in weight for iloperidone, ziprasidone and placebo were 2.8, 1.1 and 0.5 kg, respectively. Clinically significant weight gain (> 7%) occurred in 21% of patients receiving iloperidone vs. 7% with ziprasidone and 3% with placebo. Patients’ weight stabilized after Study Day 14 (when iloperidone achieved steady state).
With regard to lab values, these authors studied total cholesterol, triglycerides, glucose, and prolactin (baseline to end point). Average changes in lab values were similar across the three treatment groups; most parameters did not change much over time.

Kane et al.

The long-term safety of iloperidone was examined in three prospective, randomized, multicenter, double-blind, flexible-dose, parallel-group studies over 52 weeks (initial 6-week phase followed by a 46-week maintenance phase). Patients with schizophrenia or schizoaffective disorder and a PANSS-T score of ≥ 60 were randomized to receive either iloperidone 4-16mg/d or haloperidol 5-20mg/d. The primary outcome was time to relapse (defined as ≥ 25% increase in PANSS-T; discontinuation for lack of efficacy; aggravated psychosis with hospitalization; or ≥ 2 point increase in CGI-C). Secondary outcomes included change from baseline in PANSS-T, BPRS and CGI-C scores. Safety endpoints included adverse events, EPS and akathisia. Baseline characteristics were similar between groups with a mean age of 35 years, ~60% male and ~ 80% with previous hospitalizations. The mean dose at the end of 6 weeks was 11.8 mg/d for iloperidone and 13.2 mg/d for haloperidol. Overall 1,326 patients completed the 6-week phase; of which 371 (36.6%) receiving iloperidone and 118 (37.8%) receiving haloperidol exhibited a treatment response and were eligible to continue in the long-term phase.

At the end of the long-term 46-week maintenance phase there were similar rates of relapse between the groups; 43.5% with iloperidone and 41.2% with haloperidol (HR 1.03; 95% CI, 0.74-1.43; p=0.86). The mean time to relapse was 89.8 days with iloperidone and 101.8 days with haloperidol (p=0.84). There was no difference between iloperidone and haloperidol in the mean adjusted change in the PANSS-T score (-16.1 vs. -17.4, respectively; p=0.34) nor the mean adjusted change in BPRS (-9.0 vs. -9.6, respectively; p=0.39). Discontinuation rates due to adverse events were 4.3% with iloperidone and 8.5% with haloperidol. As compared to haloperidol, iloperidone exhibited significantly less EPS as measured by the ESRS rating scale (-1.6 vs. 0.6; p<0.001). It was also associated with less worsening of akathisia (9.2% vs. 23.7%; p<0.001). Patients receiving iloperidone experienced slightly greater weight gain (3.8 vs. 2.3kg) as well as increases in total cholesterol (0.89 mg/dl), triglycerides (6.82 mg/dl) and glucose (2.66 mg/dl). Increases in the QTc interval were similar between the two groups, 10.3 msec with iloperidone and 9.4 msec with haloperidol. Investigators concluded that iloperidone demonstrated long-term efficacy equivalent to haloperidol with a favorable safety profile, making it a reasonable option for maintenance therapy in schizophrenia.

**DRUG INTERACTIONS**

Iloperidone is extensively metabolized by CYP3A4 and CYP2D6. Inhibitors of CYP3A4 (i.e. ketoconazole, clarithromycin) or CYP2D6 (i.e. fluoxetine, paroxetine) can inhibit iloperidone elimination and cause increased blood levels. In preclinical pharmacokinetic trials, co-administration of one dose of iloperidone 3 mg with ketoconazole increased the
AUC of iloperidone and its metabolites P88 and P95 by 57%, 55% and 35%, respectively. Similarly, co-administration of iloperidone with paroxetine increased the mean steady-state peak concentrations of iloperidone and its metabolite P88, by about 1.6 fold, and decreased mean steady-state peak concentrations of its metabolite P95 by one-half. Iloperidone doses should be reduced by about one-half when administered with strong inhibitors of CYP3A4 and CYP2D6. When the CYP3A4 and/or CYP2D6 inhibitor is withdrawn from the combination therapy, iloperidone dose could then be increased to the previous level.

There may be possible potentiation of QTc prolongation when iloperidone is administered with Class 1A (i.e. quinidine, procainamide) or Class III (i.e. amiodarone, sotalol) antiarrhythmics, antipsychotic medications, antibiotics (i.e. moxifloxacin) or other classes of medication known to prolong the QTc interval (i.e. methadone).

**COST**

**CONCLUSION**

Iloperidone appears to be both safe and effective in the treatment of schizophrenia. Although long-term data are limited it also appears that iloperidone appears to be as effective as haloperidol for preventing relapse in individuals with this disorder.

**RECOMMENDATIONS**

Iloperidone has unique receptor-binding characteristics with possible anxiolytic/antidepressant properties, a favorable EPS profile, and metabolic effects similar to those of risperidone. Of special interest is the fact that iloperidone’s akathisia rate is comparable to that of placebo.

On the down side, iloperidone does not appear to be any more efficacious than currently available atypical antipsychotics and current package labeling does not recommend iloperidone as a first line agent. The iloperidone registration trials included patients on haloperidol, ziprasidone, and risperidone; these were included to monitor study sensitivity. If a study didn’t show a statistical benefit for either the iloperidone or positive control group compared to the placebo group, that study would be considered a failed trial and would not be considered further. Statistical comparisons between active treatments are not appropriate as they are not part of the research design and are underpowered. In 2008, the FDA issued a not approvable letter for iloperidone, basing its decision on iloperidone’s questionable efficacy versus risperidone. Another concern with the use of iloperidone is that its QTc prolongation is thought to be affected by metabolic inhibition (at 2D6 and 3A4) and an individual’s CYP2D6 status (EM versus PM).

It’s possible that expanded use of iloperidone will more clearly define its role in therapy but at present, it’s difficult to predict the true clinical significance of the aforementioned
clinical variables. We would recommend adding it to the formulary with restrictions. One possible restriction is that its use be limited to individuals who have failed previous antipsychotic trials because of akathisia.
References


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