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EXPERT REVIEW

Iloperidone: Efficacy Review for the Acute Treatment of Schizophrenia in Adults

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Abstract: Iloperidone is one of the newest second generation antipsychotic medications approved in the United States for the acute treatment of schizophrenia in adults. Iloperidone binds tightly to serotonin-2A ($5HT_{2A}$) and dopamine-2 (D_2) receptors with very little affinity to histamine-1 (H_1) and muscarinic-1,2 (M_{1-2}) receptors. The efficacy of iloperidone for the treatment of schizophrenia has been established in three 6 week trials, one 4 week trial, and three 52-week follow-up studies. Iloperidone is generally well tolerated. The most common adverse effects observed in clinical studies of iloperidone are dizziness, weight gain, sedation, tachycardia, and orthostatic hypotension. This medication may serve as an additional treatment option for patients with schizophrenia.

Keywords: antipsychotic, schizophrenia, efficacy

Introduction

Schizophrenia occurs in roughly 20 million people world-wide with a lifetime risk of 0.3% to 2%.[1] This condition causes a substantial burden to the affected patient and his or her family due to the severity of symptoms.[2] Patients with schizophrenia require long-term support in activities of daily living due to the impact of the positive, negative, and cognitive symptoms associated with this illness. There is also a large economic impact of this condition due to the effects on healthcare resource consumption, ability to work, and personal income.[2]

One of the major determinants of cost in schizophrenia is relapse of illness.[3] Some of the components of cost include acute hospitalization and increased need for outpatient services and medications. Although there are currently several antipsychotic medications available on the market, results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) illustrate that antipsychotic treatment is associated with poor adherence, drug discontinuation, and frequent switching due to lack of efficacy and poor tolerability of these agents.[4,5] A recent study noted that switching of antipsychotics occurs at rates of 25%–50% during a one year time period.[6] The authors also concluded that switching antipsychotic medications leads to an increased utilization in acute care services and earlier utilization of these services than patients that were maintained on their initial antipsychotic medication throughout the period of the study. To minimize the need for frequent switching, it is prudent to tailor treatments for patients based on individual needs while closely monitoring effectiveness, safety, tolerability, and overall patient acceptance of therapy. Newer second generation antipsychotic medications with slightly different side effect profiles as compared to older agents provide additional treatment options for patients with schizophrenia.[7] Iloperidone (Fanapt™) is one of the newest second generation antipsychotic agents approved for use in the acute treatment of schizophrenia in adults by the United States Food and Drug Administration (FDA).

Pharmacodynamics

Iloperidone is a piperidinyl-benzisoxazole derivative, with structural similarities and differences as compared to other currently approved antipsychotics such as ziprasidone, risperidone, and paliperidone (see Fig. 1).[8,9] Although the exact mechanism of action of this agent is unknown at this time, therapeutic effects are speculated to be due to a combination of dopamine-2 (D_2) and serotonin-2A ($5HT_{2A}$) receptor antagonism. Several in vitro studies have characterized the receptor binding profile for iloperidone. Iloperidone has a high binding affinity to $5HT_{2A}$, D_2, and dopamine-3 (D_3) receptors and moderate affinity for dopamine-4 (D_4), serotonin-6 ($5HT_6$), serotonin-7 ($5HT_7$), and noradrenergic-α_1 receptors (NE-α1). Iloperidone possesses low or minimal binding affinity for serotonin-1A ($5HT_{1A}$), dopamine-1 (D_1), and histamine-1 (H_1) receptors with no appreciable affinity for cholinergic muscarinic
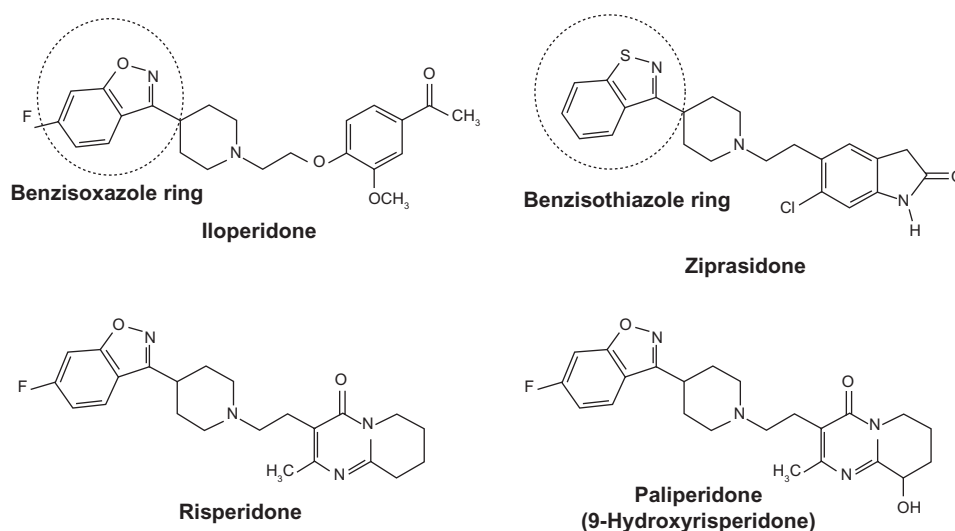

Figure 1. Chemical structures of iloperidone, ziprasidone, risperidone, and paliperidone.

receptors. Iloperidone has two active metabolites (P88 and P95) that also possess moderate to high affinity for D_2, $5HT_{2A}$, $5HT_{2C}$, NE-α1, and H_1 receptors.[10,11]

Pharmacokinetics

Oral iloperidone is rapidly and extensively absorbed with a relative bioavailability of 86%.[8] Peak plasma concentrations occur within 2–4 hours of dose ingestion. When taken with food, the TMax is delayed, but the overall exposure to iloperidone and its metabolites is not significantly altered.[12] Steady state levels are attained within 3–4 days after reaching stable doses. Iloperidone is hepatically metabolized by three different pathways in the liver: carbonyl reduction, hydroxylation via CYP2D6 and *O*-demethylation via CYP3A4.[8,9] The mean half-lives of the P88 and P95 metabolites differ in patients with a CYP2D6 poor metabolizer genotype as well as in those patients taking a potent CYP2D6 inhibitor such as paroxetine or fluoxetine.[8] The half-lives of the parent drug, P88, and P95 in extensive metabolizers are 18, 26, and 23 hours, respectively, while the half-lives in poor metabolizers are 33, 37, and 31 hours. At this time, iloperidone is not recommended for use in patients with hepatic impairment due to the potential accumulation of the P88 metabolite as compared to healthy volunteers.[8]

Clinical Efficacy
Short-term studies
The clinical efficacy of iloperidone was investigated in four short-term and three long-term clinical studies.[13–15] Three similar phase 3 investigations initially studied the efficacy of iloperidone in the acute treatment of schizophrenia.[15] All 3 of these trials had similar designs, were conducted over a 6 week period of time, with results reported in pooled analyses.[15] The participants that were included in the trials were men and women between the ages of 18–65 years with an acute or subacute exacerbation of schizophrenia and a Positive and Negative Syndrome Scale (PANSS) score of at least 60 at screening and baseline. In Study 1, participants were randomized to receive iloperidone 4 mg/d, iloperidone 8 mg/d, iloperidone 12 mg/d, haloperidol 15 mg/d, or placebo. Study 2 randomized participants to dose ranges of iloperidone 4–8 mg/d, iloperidone 10–16 mg/d, risperidone 4–8 mg/d, or placebo. The final study randomized

participants to dose ranges of iloperidone 12–16 mg/d, iloperidone 20–24 mg/d, risperidone 6–8 mg/d, or placebo. All of the studies divided the doses of all medications into twice daily dosing which is the dosing frequency included in the approved product labeling for iloperidone. These studies supported the approval of iloperidone at doses of 12–24 mg/d.[8]

Study 1 used a primary efficacy endpoint of the change from baseline to endpoint on the PANSS total score (PANSS-T) while the other 2 studies used scores on the 18-item Brief Psychiatric Rating Scale (BPRS) as the primary outcome measure.[15] Secondary outcome measures included changes from baseline to each post baseline assessment on the PANSS Positive and Negative Subscales (PANSS-P and PANSS-N), as well as the General Psychopathology Subscale (PANSS-GP), and on the BPRS. Clinical Global Impression of Severity (CGI-S) was also evaluated in studies 2 and 3.

All 3 studies based efficacy analyses on the intent-to-treat (ITT) population which means that all study participants that received at least 1 dose of study medication and completed at least 1 post baseline PANSS assessment were included in the analyses.[15] The primary goal for all studies was to assess the efficacy of iloperidone versus placebo. In Study 1 the mean results for the iloperidone 8 mg and 12 mg groups combined were compared to placebo. In Study 2, the placebo comparison was made between the iloperidone 10–16 mg/d group and placebo, and the iloperidone 12–16 mg/d group was compared to placebo in Study 3. An additional post hoc analysis was carried out for all 3 studies to assess participants who had reached steady-state therapeutic doses of iloperidone for more than one week of treatment. This was done to assess the influence of the relatively slower (2 weeks) time to reach a steady-state dose of iloperidone due to the slow titration schedule as compared to the active comparators which was thought in retrospect to have disproportionately influenced the drop-out rates such that more iloperidone subjects were lost due to perceived loss of efficacy in the earlier stages of treatment. This analysis pooled results across studies for participants treated with iloperidone 4–8 mg/d, iloperidone 10–16 mg/d, iloperidone 20–24 mg/d, risperidone 4–8 mg/d, and placebo. It also included data from participants that were treated with haloperidol 15 mg/d and evaluated changes in

BPRS and other efficacy measures for all participants that remained on treatment for at least 2 weeks.

The baseline demographic and clinical characteristics were similar between the groups across all 3 studies.[15] Most participants were in their late 30's or early 40's, and the majority of the study sample consisted of Caucasian males. Most of the participants had a Diagnostic and Statistic Manual-IV (DSM-IV) diagnosis of schizophrenia and 20%–37% with a diagnosis of schizoaffective disorder.

Across the 3 studies, a total of 1,943 participants were randomized to iloperidone, haloperidol, risperidone, or placebo.[15] In Study 1 the PANSS-T score improved significantly in the iloperidone 12 mg group (9.9 point improvement on the PANSS-T) and in the haloperidol 15 mg/d group (13.9 point improvement on the PANSS-T) while changes in the PANSS-T score in the iloperidone 4 mg (9 point improvement) and iloperidone 8 mg (7.8 point improvement) groups did not statistically separate from placebo (4.6 point improvement). Significant decreases in baseline BPRS score were seen in Study 2 for the iloperidone 4–8 mg group (6.2 point improvement), iloperidone 10–16 mg group (7.2 point improvement), and the risperidone 4–8 mg group (10.3 point improvement) versus placebo (2.5 point improvement). While there was improvement in BPRS scores for all of the groups in Study 3, significant improvement was only noted in the iloperidone 20–24 mg group (8.6 point improvement) and in the risperidone 6–8 mg group (11.5 point improvement) when compared to placebo (5 point improvement).

Due to the large range of doses used in these first three studies, a post-hoc analysis was completed to increase the statistical power and the ability to detect differences across dose strata. Participants were included in the post hoc analysis if they had remained on double-blind treatment for at least two weeks.[15] One thousand five hundred fifty three of the 1943 randomized participants were included in the combined post hoc analysis. Change in mean baseline BPRS scores was significant for all dose ranges of iloperidone (4–8 mg/d −7.9 points, 10–16 mg/d −9.2 points, 20–24 mg/d −10.0 points) as well as haloperidol 15 mg/d (11.4 points) and risperidone 4–8 mg/d (11.9 points) when compared to placebo (5.4 points).

A review of secondary outcome measures showed a significant improvement of 11% from baseline to endpoint BPRS score for only the iloperidone 12 mg/d group in Study 1.[15] No significant differences were seen for the iloperidone 4 mg/d or 8 mg/d groups for any of the secondary outcome measures, and the haloperidol group showed significance on all of the measures. In Study 2, significant improvement was seen on all of the PANSS subscales, with the exception of the PANSS-N scale and on the CGI-S for the iloperidone 4–8 mg/d group. In the iloperidone 10–16 mg group, significant improvement was seen on all PANSS subscales as well as the CGI-S scores. In Study 3 only the CGI-S score significantly improved in the iloperidone 12–16 mg/d group and all PANSS subscale scores and the CGI-S improved in the 20–24 mg group.

Based on the results from these pooled data, it was concluded that iloperidone at doses ranging from 4 mg/d to 24 mg/d are effective in treating the various symptoms of schizophrenia on an acute basis. Higher doses seemed to result in numerically better improvement from baseline but these studies were not powered to detect statistical differences between doses. In these studies, the results of the post hoc analysis differed from the ITT last observation carried forward (LOCF), as this type if design may increase bias when reasons for discontinuation differ across treatment groups. It should also be noted that doses of the active comparators (haloperidol and risperidone) were on the higher side of those commonly used clinical practice, and the high dosing may have accounted for better efficacy with higher rates of extrapyramidal symptoms (EPS). Therefore, an additional phase 3 study was designed to provide additional information about the safety and efficacy of iloperidone.

The final registry study investigating iloperidone for the acute treatment of schizophrenia was a 4 week trial to evaluate efficacy, tolerability and safety of iloperidone 24 mg/d versus placebo using ziprasidone as an active comparator.[13] This investigation was designed as a multicenter study at 35 sites in the US and 9 sites in India. Men and women aged 18–65 were eligible for inclusion if they had a DSM-IV diagnosis of schizophrenia. Note that there were no schizoaffective participants in this study, which is a difference from the earlier registry trials. Participants also needed to have a CGI-S score >4 at baseline, a PANSS-T score of 70 or

greater at screening and baseline, and a rating of 4 or greater on two of the PANSS-P symptoms (delusions, conceptual disorganization, hallucinations, and suspiciousness/persecution) at screening and baseline. Thus, potential participants for this study were more ill than those enrolled in earlier studies. Additional exclusion criteria included a diagnosis or history of chemical dependence, congenital long QT syndrome, and clinically significant gastrointestinal, hepatic, or renal disease. Potential participants were also excluded if they had a history of being non-responsive to antipsychotic treatments, or other medical conditions that presented risks during a clinical trial situation.

This was a prospective, randomized, double-blind, placebo- and active-controlled, multicenter study. Participants were randomized to iloperidone, ziprasidone, or placebo. Both medications and placebo were administered twice daily. Iloperidone was titrated to 24 mg/d and ziprasidone was titrated to 160 mg/d. All participants included in the study were hospitalized for the titration and maintenance periods.[13] Treatment consisted of a 14 day screening period, a 1 week titration period, and a 3 week maintenance period. Assessments were performed at the baseline visit, and then participants were randomly assigned to medication starting on the morning of day 1. The medications were titrated from days 1 through 7 with daily assessments during the titration period. After initial titration, assessments were completed on days 10, 14, 21, and 28 during the maintenance period and/or at discontinuation/termination. This study did not include a placebo wash out period, and participants could continue current antipsychotic medication up to day 0. Adjunctive treatments were allowed for treatment of insomnia, agitation, restlessness, and treatment of EPS if needed.

The primary efficacy measure was change from baseline in PANSS-T score.[13] Secondary variables included change from baseline on the BPRS, PANSS-P, PANSS-N, PANSS-GP, Calgary Depression Scale for Schizophrenia (CDSS), CGI-S, and Clinical Global Impression of Change (CGI-C). Safety end points included incidence of treatment emergent adverse effects (TEAEs), and changes from baseline in EPS as measured by the Extrapyramidal side effect rating scale (ESRS) and Barnes Akathisia Rating Scale (BAS). Vital signs, electrocardiography

measures, weight, and laboratory values were also measured.

All participants who received 1 or more doses of study medication and underwent baseline screening and 1 or more PANSS baseline efficacy evaluations were included in the modified ITT population.[13] A mixed-effects model repeated measures (MMRM) was used to analyze the primary efficacy endpoint. LOCF was used to account for missing data. All participants that received at least 1 dose of medication and had at least 1 subsequent safety evaluation were included in the safety analysis. The frequency of TEAEs, abnormal vital signs, and lab values were summarized in the results. Change from baseline in ESRS subscales of 1 point of greater were compared.

A total of 593 participants were randomized.[13] Baseline characteristics were similar between the groups with a mean age of approximately 40 years. The majority of the participants were men and of African American race. There was a statistically significant decrease in PANSS score by 12 points in participants in both the iloperidone and ziprasidone group when compared to placebo. Significant differences in PANSS-P were seen as early as 14 days for iloperidone and as early as 10 days for ziprasidone. Significant changes were also noted on the PANSS-N for iloperidone as early as 14 days and for ziprasidone at all assessments when compared to placebo. No differences were noted for either medication on the PANSS-GP scale at any time point. Improvement on CGI-S was noted at week 14 and beyond for both medications compared to placebo. There was no significant improvement on the CDSS scores when compared to placebo for either of the active comparators.

Long-term studies

Three hundred seventy-one schizophrenia and schizoaffective disorder subjects randomized to iloperidone and 118 haloperidol-treated subjects also participated in long-term extensions of three initial safety and efficacy studies.[14] These subjects were initially enrolled in six-week efficacy studies, and subsequently continued on to a 46-week follow-up with time to relapse as the primary outcome variable assessed in a combined single long-term analysis. Relapse included hospitalization due to schizophrenia

symptoms, lack of efficacy leading to medication discontinuation, or significant (10 point, or >25%) increases in PANSS-T scores from the beginning of the long-term treatment phase. Relapse rates and the time to relapse and time to discontinuation did not significantly differ between iloperidone and haloperidol.

Safety and Tolerability

Adverse events characterized during the acute treatment phase with iloperidone have been described in a combined analysis of the early phase three studies using haloperidol and risperidone as active controls[16] and separately for the ziprasidone active control study.[13] Overall, in the early phase three studies, 3.9%–5.6% of iloperidone-treated subjects discontinued treatment due to a reported adverse event, as opposed to 7.6% of haloperidol, 6.2% of risperidone, and 4.8% of placebo-treated participants.[16] EPS in iloperidone-treated subjects improved from baseline, worsened in haloperidol-treated subjects, with mixed changes in the risperidone groups. Akathisia significantly worsened for haloperidol-treated participants, but did not differ from placebo in the iloperidone or risperidone-treated individuals. Tremor and general EPS were most commonly observed in the haloperidol groups at rates of 20%–22%.

The most common side effect associated with iloperidone in early studies[16] was dizziness, which occurred in ~10%–12% of those treated with 4–16 mg/d and 23.2% of those treated with 20–24 mg/d. The related measure of orthostasis followed similar trends, occurring in 19.5% of all iloperidone-treated participants, 15.3% of haloperidol-treated participants, 12% of risperidone-treated participants, and in 8.3% of the placebo group. Interestingly, objective measures of orthostasis were observed in the lower treatment strata of iloperidone (19.4%–21.2% of those treated with 4–16 mg/d) which may represent initial sensitivity to this effect during the early stages of titration. QTc interval changes ranged from 2.9–9.1 msec in iloperidone-treated participants with the most robust changes occurring in those treated with 20–24 mg/d. Weight gain in these studies ranged from 1.5–2.1 kg in those treated with iloperidone, 1.5 kg in those treated with risperidone, −0.1 kg in those receiving haloperidol

and −0.3 kg in those in the placebo groups. These results represent a small, yet significant separation from placebo for both the iloperidone and risperidone treatment groups.

In the most recent 4 week study that utilized ziprasidone as an active control, adverse events resulted in discontinuation for 5% of iloperidone participants, 8% of ziprasidone participants, and 8% of placebo participants with psychotic symptoms being the most commonly mentioned reason for cessation of treatment.[13] When EPS data were analyzed, both iloperidone and ziprasidone treated subjects had significant improvement on these ratings after treatment. Iloperidone did not result in significant worsening versus placebo on any EPS subscale, but ziprasidone was noted to be associated with significant worsening of parkinsonism and akathisia. The differences in akathisia ratings between ziprasidone and placebo were significant by day 14 and remained significant through the study endpoint.

In this study, the most common treatment-emergent adverse effects noted in the iloperidone group included dizziness (51%), sedation (38%), weight gain (34%), tachycardia (28%), dry mouth (26%), increase in heart rate (24%), nasal congestion (25%), and orthostatic hypotension (21%).[13] Significant weight gain, as defined as ≥7% increase from baseline was noted in 21% of the iloperidone group, 7% of the ziprasidone group, and 3% of the placebo group. Mean changes in triglycerides were 0.8 mg/dL, 4.6 mg/dL and 19.5 mg/dL for iloperidone, ziprasidone, and placebo respectively, and the percentages of participants having glucose values outside the upper limit of normal were 13.6%, 11.3%, and 8% when the 3 groups were compared. Prolactin levels were elevated outside of the normal range for 14.8% of iloperidone participants, 9.5% of ziprasidone participants, and 1.5% of placebo participants. Change in QT interval at day 14 was similar in iloperidone and ziprasidone-treated subjects (11.4 and 11.3 msec, respectively), which were both separated from placebo. By day 28 these values decreased to 7 msec for iloperidone and 5.2 msec for ziprasidone.

Pharmacogenomics

During clinical trials of iloperidone, DNA was collected for additional studies of genetic

predictors of response and side effects. While many pharmaceutical compares now do this, these efforts for iloperidone were significant and illustrate the knowledge that can be gained from targeted candidate gene studies juxtaposed with whole genome analyses to identify and further characterize known or novel genetic contributors to drug outcomes. Through these investigations, genetic polymorphisms in the neuronal pas domain protein-3 gene (*NPAS3*) which encodes a transcription factor that may be involved with the regulation of molecular pathways involved with schizophrenia were identified as potential predictors of response to iloperidone.[17] Additionally, markers in the XK Kell blood group complex subunit-related family member 4 gene (*XKR4*), glutamate receptor ionotropic AMPA4 gene (*GRIA4*), glial cell-line derived neurotrophic factor receptor-alpha 2 gene (*GFRA2*), and the nucleoside diphosphate linked moiety X)-type motif 9 pseudogene 1 gene (*NUDT9P1*) which is located near the serotonin-7 receptor gene (*HTR7*) were found to be associated with response to iloperidone.[17] Additionally, the ceramide-like kinasase gene (*CERKL*), the solute carrier organic anion transporter family, member 3A1 gene (*SLCO3A1*), the bruno-like 4 gene (*BRUNOL4*), the neuregulin 3 gene (*NRG3*), the nucleotide-binding protein-like gene (*NUBPL*), and the palladin gene (*PALLD*) were found in a separate investigation of genetic predictors of QTc prolongation from iloperidone.[18] The clinical implications of these findings remain to be seen, but if population subgroups are identified that have differential benefit-to-risk ratios that are informed by genetics, this will be a significant advance in how we conceptualize drug and dose selection for participants requiring antipsychotic therapy.

Conclusions and place in therapy

Iloperidone is a second generation antipsychotic approved by the FDA. Its mechanism of action is similar to other currently available second generation antipsychotics, although subtle differences in the receptor binding of this agent are thought to result in a somewhat unique side effect profile that may distinguish it from other currently approved drugs for schizophrenia. Phase two and three studies to date have compared iloperidone to placebo using active control agents (haloperidol, risperidone, and ziprasidone) for assay sensitivity in these trials. Iloperidone appears to be more effective than placebo for the treatment of acutely exacerbated schizophrenia, particularly in those who are able to tolerate the slower titration needed for this drug due to dizziness and orthostasis that may be bothersome, particularly early in treatment.

Disclosures

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