## Iloperidone For the Treatment of Schizophrenia—Selected Posters

Over 50% of schizophrenia patients drop out of controlled trials within 6 months due to lack of efficacy or in some cases tolerability issues [Liu-Siefert et al. *BMC Med* 2005; Lieberman JA et al. *N Engl J Med* 2005], particularly extrapyramidal symptoms (EPS), akathisia, weight gain, metabolic effects, sedation, and anticholinergic effects. EPS and akathisia effects carry an increased risk of suicide [Dong JY et al. *J Affect Disord* 2005] and poor adherence, while metabolic effects can increase the risk for diabetes and cardiovascular disease. Iloperidone, a mixed D2/5-HT2 antagonist that is under FDA review, may provide a lower EPS/akathisia liability.

A combined analysis of three 52-week studies that compared the efficacy of iloperidone (4-16 mg/day) versus haloperidol (5-20 mg/day) in schizophrenia patients showed that 36.4% of patients in each treatment group had discontinued [Torres R et al. NR4-093]. Relapse occurred in 43.5% of the iloperidone and 41.2% of the haloperidol patients. Improvement in the CGI-C scores occurred in 65% of iloperidone and 66% of haloperidol patients. Iloperidone was non-inferior to haloperidol [HR 1.03, 95% CI 0.74, 1.43; p=0.86]. Safety results from this study [Wolfgang CD et al. NR4-024] showed that 4.3% of iloperidone patients versus 8.5% of haloperidol patients discontinued because of an adverse event. Fewer iloperidone patients experienced worsening of their EPS or akathisia scores versus haloperidol (Figure 1).

Figure 1. Patients (%) With Worsening EPS and Akathisia From Baseline to Endpoint.

*p<0.001 versus haloperidol.
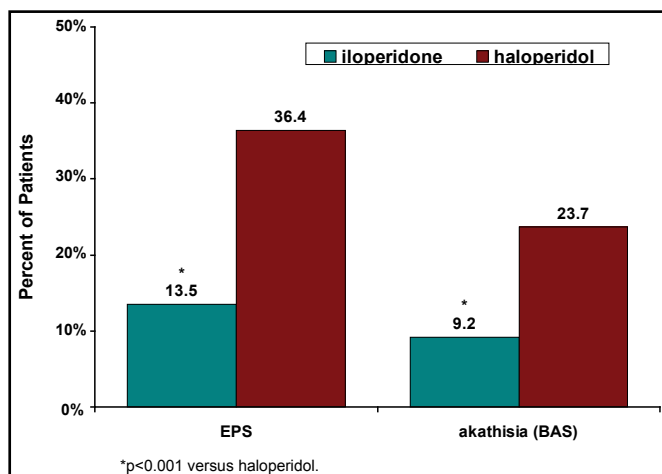
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Efficacy results of a 28-day phase 3 trial [Weiden PJ et al. NR4-078] showed significant decreases in PANSS scores for patients who were treated with iloperidone 12 mg BID (-12.0; p=0.006) or ziprasidone 80 mg BID (-12.3; p=0.012) versus placebo (-7.3). Safety results [Hamilton J et al. NR4-046] showed discontinuation rates of 35%, 34%, and 40% for iloperidone, ziprasidone, and placebo, respectively. Adverse events that were associated with iloperidone included dizziness, sedation, and modest weight increase versus sedation, dizziness, and akathisia for ziprasidone. A significantly (p<0.05) higher percentage of ziprasidone patients experienced worsening of EPS scores and akathisia versus placebo, a finding that was not noted with iloperidone.

Pooled data from 9 phase 2 and 3 clinical trials showed that iloperidone, haloperidol, ziprasidone, and risperidone produced similar weight gains in patients [Stahl SM et al. NR4-102]. The percentage of patients who had a ≥7% change in body weight was 23.2% for iloperidone, 17.6% haloperidol, 14.2% risperidone, and 7.4% ziprasidone (short-term study only). Iloperidone demonstrated favorable metabolic effects on glucose, cholesterol, and triglycerides, and unlike risperidone and haloperidol, it was not associated with hyperprolactinemia. Lauriello J et al. (NR4-050) reported that iloperidone use had fewer incidences of EPS and akathisia versus the other antipsychotics that were tested.

In general, the researchers in these studies concluded that iloperidone was as effective as the existing antipsychotic treatments for schizophrenia but may be associated with a lower incidence of EPS/akathisia.

Aripiprazole For the Treatment of Schizophrenia—Selected Posters

The goals for the management of schizophrenia and schizoaffective disorders are to decrease severity and frequency of psychosis and associated mood symptoms while reducing the inherent risks of antipsychotic medications. Aripiprazole demonstrates agonist activity toward dopamine D2 and 5-HT1a receptors and antagonizes 5-HT2a receptors, sites that are associated with psychosis and mood disorders. Its moderate-to-lack of affinity for histamine H1 and cholinergic muscarinic receptors suggests a favorable safety profile.

Pooled data from two 52-week efficacy studies that compared aripiprazole (20-30 mg/day) with haloperidol (7-10 mg/day) in patients with early (aged ≤40 years with first episode and duration of illness ≤60 months) schizophrenia [Crandall D et al. NR4-028] showed that significantly (p=0.001) more of the haloperidol (29%) patients discontinued treatment versus aripiprazole-treated patients (11%). Remission rates, defined by the Remission in Schizophrenia Working Group, were significantly higher with aripiprazole (38% vs 22%; p=0.003) and were achieved in a shorter time versus haloperidol.

In another study that compared aripiprazole treatment (mean 23.9 ± 6.4 mg/day) with placebo in patients with schizoaffective disorder, Glick ID et al. (NR4-039) reported fewer discontinuations with aripiprazole (42%) versus placebo (57%). PANSS total score was significantly (p<0.05) improved after 3-4 weeks of aripiprazole treatment versus placebo (Figure 1). Adverse events were similar and included anxiety, vomiting, dizziness, akathisia, tremor, and depression. Although EPS symptoms and metabolic values were similar, prolactin levels decreased more in the aripiprazole group (-5.6 vs -1.3; p<0.0001).

Figure 1. Mean Change from Baseline to Endpoint in the PANSS Total Score.

At Weeks 3 and 4 aripiprazole significantly (p<0.05) differed from placebo.
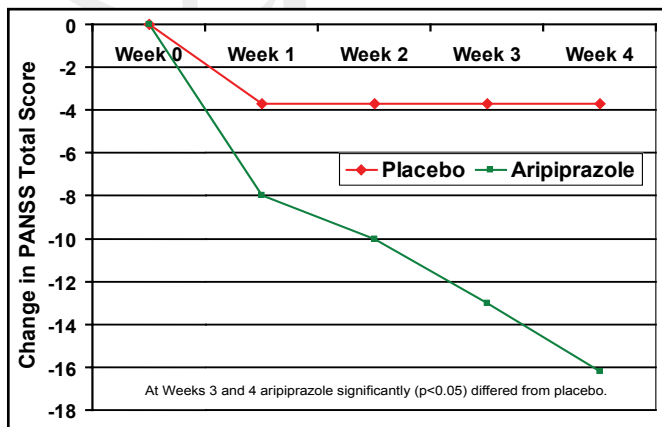
At Weeks 3 and 4, aripiprazole differed significantly (p<0.05) from placebo
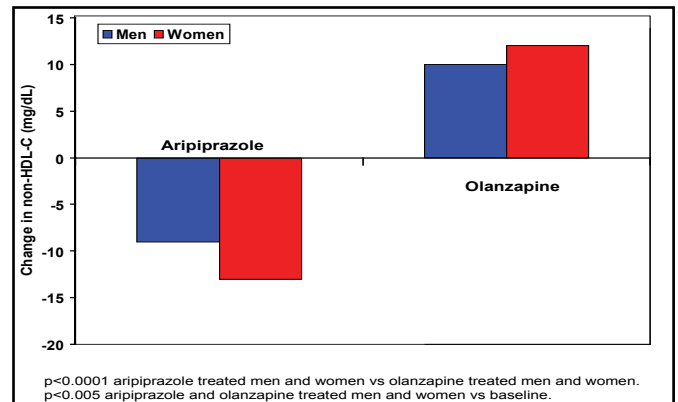
In a pooled analysis of data from 5 studies, Kane JM et al. (NR4-097) noted significant decreases in PANSS total score after 4 weeks of treatment with aripiprazole (5-30 mg/day) versus placebo (-14.4 vs -2.4; p=0.001). The largest effect was noted for the hostility and uncooperativeness symptom domains.

In a further analysis of the above data and symptom domains, Janicak P et al. (NR4-080) reported that negative, positive, depression/anxiety, disorganized thought, and hostility domains significantly (p<0.05)

improved after aripiprazole treatment versus placebo beginning at Week 2 in patients who were diagnosed as schizophrenic or having schizoaffective disorder.

Meyer JM et al. [NR4-053] noted that non-HDL cholesterol, a strong predictor of cardiovascular disease (often associated with schizophrenia treatment), significantly (p<0.001) decreased after aripiprazole treatment versus significant (p<0.001) increases after olanzapine treatment (Figure 2).

Figure 2. Mean Change in Non-HDL at Week 26.

p<0.0001 aripiprazole treated men and women vs olanzapine treated men and women.
p<0.005 aripiprazole and olanzapine treated men and women vs baseline.

In general, the investigators concluded that aripiprazole appears to be an effective first-line treatment for schizophrenia symptoms that has a favorable adverse event profile.

Hippocampal Volume Predicts Conversion to Dementia in Patients with Mild Cognitive Impairment

In a study that had a 5-year follow-up, hippocampal volume (HV) was shown to be correlated with elevated risk in a cohort of elderly patients with mild cognitive impairment. Individuals who developed dementia had a smaller HV at baseline.

Patients with minimal cognitive impairment (MCI) as identified by the Clinical Dementia Rating scale (CDR) are known to have a conversion rate to dementia of 20%. The CDR Sum of Boxes score (CDR-SB; range 0-18) enables a quantitative evaluation of that impairment. To evaluate HV as a predictor of conversion, this study assessed 28 elderly patients who had a range of impairment at baseline. Impairment was gauged with the instruments of CDR-SB, MMSE (mini mental state examination), and ADAS-cog