Ziprasidone as Adjunct Therapy to Mood Stabilizers for the Treatment of Bipolar I Disorder

When used as adjunctive treatment to the mood stabilizers lithium or valproate, ziprasidone was equally effective in stabilizing mild to moderately ill subjects and severely ill subjects with bipolar I disorder (BP I). In a Phase III, randomized, double-blind, placebo-controlled trial that evaluated the efficacy of adjunct ziprasidone therapy with a mood stabilizer in the long-term maintenance treatment of BP I, patients were stratified according to baseline illness severity (as determined by Mania Rating Scale [MRS] score). This study was designed using two phases: Phase 1 consisted of open-label ziprasidone 80 to 160 mg daily, added to lithium or valproate therapy after at least 2 weeks of stabilized therapeutic serum concentration, moving on to Phase 2 once symptom stability was achieved (defined as Clinical Global Impression of Improvement [CGI-I] score ≤3) for ≥8 consecutive weeks; Phase 2 consisted of double-blind treatment with ziprasidone versus placebo in addition to lithium or valproate therapy. Analysis was performed using Fisher exact test and assessed stabilization and relapse rates, based on disease severity.

This study included patients with documented BP I and an MRS score ≥14 if they were taking lithium or valproate for ≥2 weeks or ≥18 if they were not taking lithium or valproate or if they were on an alternative mood stabilizer regimen at initial visit (with scores ≥2 on at least 4 items). Subjects who were on an alternative mood stabilizer regimen were switched to lithium (0.6-1.2 mEq/L) or valproate (50-125 µg/mL) at initial visit, and all psychotropic medications were discontinued prior to the initial visit, with the exception of lithium or divalproex sodium and lorazepam or zolpidem tartrate. Patients with clinically relevant laboratory findings; positive urine screening for morphine, cocaine, or amphetamines; or ultrafast rapid cycling (defined as ≥8 mood episodes over the past year) and those who were at risk of harming themselves or others were excluded from participation. Drug exclusions included clozapine (within 12 weeks), a depot antipsychotic (within 4 weeks), a monoamine oxidase inhibitor (within 2 weeks), or previous participation in a study that included ziprasidone.

Rates of stabilization for those with baseline MRS scores <30 were comparable with those with baselines MRS scores >30 (p=0.90). Stabilization rates were also similar for those with baseline MRS scores <26 and ≥26 (p=0.64). Among the subjects with baseline MRS scores of <30, those who were taking ziprasidone demonstrated a lower incidence of relapse compared with placebo (18.4% vs 31.6% for placebo; p=0.04). This was also the case for subjects with baseline MRS scores <26 who were taking ziprasidone (15.1% vs 34.1% for placebo; p<0.01). Relapse rates for subjects with baseline MRS scores of ≥26 were slightly higher for those who were taking ziprasidone (32.4%) compared with placebo (28.6%), but this difference was not statistically significant (p=0.79).

According to these findings, the use of adjunct ziprasidone therapy with either lithium or valproate was equally effective in stabilizing mild to moderately ill subjects and severely ill subjects with BP I. While mild to moderately ill patients who took ziprasidone (in addition to lithium or valproate) had a lower incidence of relapse, there was little difference in relapse rate among severely ill patients who were taking ziprasidone compared with placebo. Detailed safety data were not provided in this poster presentation.

Highlights from the
American Psychiatric Association 163rd Annual Meeting