A Double-Blind, Randomized Comparative Study of Aripiprazole and Olanzapine in Patients with Schizophrenia

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Background: Few studies have directly compared the efficacy and tolerability of atypical agents.

Methods: This multicenter, randomized, double-blind study compared the efficacy and tolerability of aripiprazole ($n = 355$) with olanzapine ($n = 348$) in patients with schizophrenia experiencing acute relapse. After a 6-week acute treatment phase, patients with Clinical Global Impression—Improvement = 1–3 or ≥ 20% reduction in the Positive and Negative Symptom Scale (PANSS) Total score could progress to the 46-week outpatient extension phase. Co-primary study objectives were to compare efficacy at Week 6 and weight gain liability from baseline to Week 26.

Results: The mean olanzapine dose was 15.4 mg/day compared with a mean aripiprazole dose of 23.0 mg/day. More patients treated with olanzapine (47%) completed the 52-week study than those treated with aripiprazole (39%); time to discontinuation was significantly in favor of olanzapine ($p < .05$). At Week 6, mean change in PANSS Total score (olanzapine, −29.5; aripiprazole, −24.6 [random regression model]) showed a treatment difference of 4.9 points. As the pre-specified non-inferiority margin (6 points) was within the 95% confidence interval (2.2–7.6) for treatment difference, olanzapine proved to be superior to aripiprazole on this measure. More patients experienced significant weight gain at Week 26 with olanzapine (40%) than with aripiprazole (21%; $p < .05$ [weighted generalized estimating equation analysis]), with significant differences observed from Week 3. Mean weight gain at Week 26 was significantly greater with olanzapine than with aripiprazole (+4.30 kg vs. +.13 kg, respectively).

Conclusions: Olanzapine had a statistically significant efficacy advantage over aripiprazole, whereas aripiprazole was associated with significantly less weight gain.

Key Words: Aripiprazole, atypical antipsychotic, olanzapine, schizophrenia, weight gain

Aripiprazole is an antipsychotic drug approved for the treatment of schizophrenia and bipolar I disorder in the United States and Europe and as adjunctive treatment to antidepressant therapy in the United States. Aripiprazole is the first approved treatment that is a partial agonist of dopamine D_2 receptors (1,2). In addition, aripiprazole has been shown to be an antagonist at type-2 serotonin (5-HT_2) receptors (3) and a partial agonist at 5-HT_{1A} receptors (4,5). It has been hypothesized that the efficacy of aripiprazole in schizophrenia is mediated through the combination of these three pharmacologic actions. In addition, aripiprazole has minimal affinity for α_2 adrenergic receptors, H_1 histamine receptors, and muscarinic cholinergic receptors (6,7); it is suggested that the lack of these activities underlies the diminished liability of aripiprazole to produce orthostatic hypotension, sedation and weight gain, and cognitive impairment, respectively.

Few long-term studies have directly compared the atypical agents (for reviews, see [8,9]). To fully understand the impact of the novel pharmacology of this agent, a long-term study was conducted to compare the efficacy and tolerability of aripiprazole with that of olanzapine, an agent that is effective for schizophrenia and associated with a significant incidence of weight gain (10). The study incorporated two primary end points: a non-inferiority analysis of efficacy at Week 6, and a superiority analysis of weight gain at Week 26.

Methods and Materials

Study Design and Patient Population

This was a multicenter, randomized, double-blind, 52-week comparative study of aripiprazole (15–30 mg/day) and olanzapine (10–20 mg/day) in patients with schizophrenia who were experiencing an acute relapse that took place between June 2000 and May 2002. Patients were randomized 1:1 with the System for Automated Randomizations (SARA). An automated touch tone system (QTONE) was used to perform the randomization and assign the appropriate medication. The randomization used a statistical blocking factor of four and was stratified by study center.

The co-primary objectives of this study were to: 1) compare the efficacy of aripiprazole and olanzapine, as measured by the Positive and Negative Syndrome Scale (PANSS) (11,12) Total score via a non-inferiority analysis at Week 6; and 2) compare the weight-gain liability of aripiprazole versus olanzapine in long-term treatment, measured by the incidence of clinically significant weight gain (≥ 7% increase) from baseline to Week 26. The study was continued to Week 52 to gather additional long-term data.

Patients (inpatients and outpatients) between 18 and 65 years of age, who were diagnosed with schizophrenia (according to the DSM-IV criteria) and were in acute relapse and who had demonstrated a previous response to antipsychotic drugs (other

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than clozapine), were eligible. In addition, patients had to have been treated as outpatients for at least one continuous 3-month period during the past 12 months and to have experienced an antipsychotic washout for a minimum of 2 days for inclusion.

Exclusion criteria included: an Axis I (DSM-IV) diagnosis of any other psychiatric disorder; prior failure to respond to olanzapine therapy; history of substance abuse; known hypersensitivity to study drugs; significant risk of suicide; recent (< one full cycle plus 1 week) treatment with a long-acting antipsychotic drug; regular use of benzodiazepines in the past 2 weeks, except low-dose sedatives.

Patients with a PANSS Total score ≥ 60, with a score of at least 4 (moderate) on two or more of the items of delusions, hallucinatory behavior, conceptual disorganization, or suspiciousness, entered an initial 6-week, double-blind, acute treatment phase. Patients were randomized to either aripiprazole (starting dose, 15 mg/day; range, 15–30 mg/day) or olanzapine (starting dose, 10 mg/day; range, 10–20 mg/day). Doses could be increased if the Clinical Global Impression Improvement (CGI-I) (13) score was ≥ 3 after at least 1 week of treatment.

Patients with a CGI-I score of 1–3 or a reduction of at least 20% in PANSS Total score at Week 6 continued outpatient treatment in the double-blind, 46-week extension phase. Flexible dosing was permitted throughout the study on the basis of efficacy and tolerability. Patients requiring hospital stay due to a worsening of schizophrenia symptoms were discontinued.

The study was conducted by 342 investigators (119 centers) in Australia, Europe, and South Africa in compliance with Good Clinical Practice (GCP). Informed consent was obtained from all patients. Institutional review board/independent ethics committee approval was received from all centers.

Concomitant Medication Use

Concomitant administration of psychotropic agents, with the exception of benzodiazepines, was prohibited. Patients could receive 4 mg/day lorazepam (or 20 mg/day diazepam) for anxiety plus 1–2 mg lorazepam (5–10 mg diazepam) if needed for sleep. No dose of lorazepam could be administered within 4 hours (12 hours for diazepam) before the administration of efficacy or safety rating scales. Weight-control therapies were also prohibited. Anticholinergic drugs for extrapyramidal symptoms (EPS) were permitted but could not exceed the equivalent of 6 mg/day benztropine or be administered within 12 hours of rating scales.

Assessments

Efficacy and safety evaluations were performed regularly throughout the study. The co-primary outcome measures were the mean change from baseline to Week 6 in PANSS Total score and the percentage of patients showing significant weight gain (≥ 7% increase) from baseline to Week 26. Secondary outcome measures included CGI-I and Clinical Global Impression Severity of Illness (CGI-S) assessments (13), mean change in body weight from baseline, and EPS rating scale assessments—Simpson-Angus Scale (14), Barnes Akathisia Scale (15), and Abnormal Involuntary Movement Scale (AIMS) (13). Laboratory values, including fasting glucose and lipids (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides) and serum prolactin, were analyzed. Vital sign assessments, physical examination, electrocardiograms, and routine laboratory tests were also performed. Adverse events (AEs) (either spontaneously reported or elicited during questioning) were reported, and their likely relationships with treatment medication (unrelated, possible, and probable) were recorded.

Statistical Methods

Sample Size and Power. Six hundred and twenty evaluable patients (310/group) were needed to yield a power of 90% to show that the true treatment difference (aripiprazole minus olanzapine) is < 6 points in the mean change from baseline to Week 6 in the PANSS Total score (co-primary outcome measure). This sample size calculation is based on a non-inferiority, one-sided test with the upper bound of the two-sided 95% confidence interval (CI), assuming a standard deviation (SD) for change from baseline to Week 6 in the PANSS Total score of 23. The rationale for using a difference of 6 points as the boundary for non-inferiority was as follows: in studies of active antipsychotic drugs such as olanzapine, risperidone, and haloperidol, the difference between active drug and placebo has typically been 12 points or greater on the PANSS Total score. The Phase III studies in the aripiprazole development program were powered to detect a placebo versus drug difference of 12 on the PANSS Total score. Therefore, 6 points represents one-half the size of a clinically meaningful difference typical for an active drug versus placebo. This strategy was suggested by Jones *et al.* (16).

With 620 evaluable patients, the power to show a true treatment difference of 15% in the percentage of patients with significant weight gain is more than 99%. This assumes that 10% of aripiprazole patients and 25% of olanzapine patients show significant weight gain at Week 26 and that the testing is two-sided at the .05 significance level. This co-primary end point was designated by amendment to the protocol before unblinding of the data, on the basis of emerging findings regarding the clinical importance of weight gain in schizophrenia and specifically with certain second-generation drugs.

Given a total of 620 evaluable patients, the power to simultaneously show a difference (aripiprazole minus olanzapine) of < 6 points in the PANSS Total score and to show a difference of 15% in the percentage of patients with significant weight gain at Week 26 (assuming that the tests of the two end points are independent) is > .9 × .99 (i.e., approximately 90%).

Efficacy Outcome Measures. A post hoc longitudinal mixed-model analysis was performed for mean change from baseline to each specified visit in the PANSS Total, mean CGI-I score, and mean CGI-S scores measures with a linear mixed model that included adjustments for baseline score, treatment, baseline score-by-week, and treatment-by-week. A spatial power covariance matrix was used to model the correlation between measurements on the same patient. The variance-covariance structure of the longitudinal profiles was modeled with random intercepts and random week effects with unstructured covariance. Hedge's G effect sizes were computed as the difference in means between treatment groups divided by the pooled SD, where the means and the pooled SD are the least square means and the square root of the residual error, respectively, estimated from the longitudinal mixed model. Analyses of response rates were performed with a weighted generalized estimating equation (WGEE) logistic model, assuming data from a binomial distribution. The WGEE model included the categorical effects of treatment, time, and treatment-by-time interaction and the continuous covariates of baseline PANSS Total score and baseline score-by-time interaction. A correlation matrix was used to model the correlation between measurements on the same patient. The probability that the patient drops out at each visit was modeled with a logistic regression model with treatment and