Efficacy and Tolerability of Aripiprazole in Patients with Schizophrenia & Schizoaffective Disorders

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ABSTRACT

Before the 1990s, treatment of psychoses centred on conventional agents whose tolerability was limited by extrapyramidal symptoms (EPS). The past decade has seen the emergence of newer generation of antipsychotic agents. These agents provide better negative symptom efficacy, less impaired cognition and lower risk of extrapyramidal syndromes. Aripiprazole, a new atypical antipsychotic drug, displayed efficacy similar to risperidone and haloperidol in numerous clinical trials. Aripiprazole does not cause significant prolactin elevation and is associated with a low rate of clinically significant weight gain compared with other atypical antipsychotics. Aripiprazole is a study drug for treating schizophrenia and has a novel pharmacologic profile. Aripiprazole provides a new treatment option with limited adverse effects for patients in need of antipsychotic therapy. The present study is a 4-week, open-labelled, randomized post-marketing clinical study conducted using aripiprazole as the study drug. Fixed doses of 15mg of the drug were administered throughout the study. A total of 249 patients with a primary diagnosis of schizophrenia or schizoaffective disorder were randomized. Efficacy measures included the Positive And Negative Syndrome Scale (PANSS) total, PANSS positive, PANSS negative and general psychopathology. Patients were evaluated for efficacy parameters at the end of 2nd week and also at the end of study. Unlike the other antipsychotics, aripiprazole was not associated with significant EPS, increase in body weight or increase in QTc interval. Aripiprazole, effective against positive and negative symptoms, is a safe and well-tolerated potential treatment for schizophrenia and schizoaffective disorder.

Keywords: Aripiprazole, schizophrenia, efficacy, safety.

Introduction

Schizophrenia is among the most serious of mental illnesses; it causes great distress to patients and their families and has a considerable social and economic impact. Globally it affects approximately 1% of the population and is a major cause of disability and is characterized by positive, negative and cognitive symptoms (Murray CJ et al, 1996; Andreasson NC, 2000). Positive symptoms are the most recognizable and include auditory hallucinations, delusions, disorganized thought, disorganized behavior, and catatonia. Negative symptoms such as alogia, flattened affect, anhedonia, and avolition are not as apparent, yet are equally disabling to the patient's functioning. A decrease in cognitive functioning has been classified as a negative symptom, but is gaining acceptance as another primary feature of the disease.

Antipsychotic medication is the main therapeutic intervention for schizophrenia. Conventional agents have been found to be effective in treating the positive symptoms of schizophrenia by reducing or eliminating symptom recurrence. Although the pathophysiology of the disease has yet to be clearly defined, antipsychotic drug development has been heavily influenced by the dopamine hypothesis, (Seeman P et al, 1990) which states that dopamine overactivity in the brain is responsible for the disease. Evidence for this hypothesis includes the capacity of antipsychotic drugs to block dopamine receptors in vivo (Anden N et al, 1970) and in vitro (Creese I et al, 1976). In addition, the clinical efficacy of antipsychotic drugs is highly correlated with their ability to block dopamine D_2 receptors (Carlsson A, 1988; Emillen G et al, 1999).

The early agents for the treatment of psychosis, the "typical" antipsychotics, were breakthrough therapies for the positive symptoms of schizophrenia but were less effective in treating the negative symptoms of the disease. In addition, the D_2 receptor antagonism of these drugs produced unwanted side effects, such as extrapyramidal symptoms (EPS) and hyperprolactinemia (Richelson E, 1999).

In attempts to meet these unmet needs, researchers have explored the possibility of using dopamine D_2 partial agonists for the treatment of schizophrenia. (Lahti AC et al, 1998; Ban TA, 2001; Iyer RN et al, 1998). The most recent class of drugs, known as "atypical" antipsychotics, was first recognized in the US with the introduction of clozapine in 1989 (Ban TA, 2001). These atypical antipsychotics,

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introduced in the mid-1990s, combined D_2 blockade with antagonism of serotonin 5-HT_{2A} receptors and produced significantly less EPS and hyperprolactinemia than the typical antipsychotics. The atypical agents that have been available in the US market after clozapine included risperidone, olanzapine, quietiapine, and ziprasidone. These agents focus mechanistically on antagonizing postsynaptic dopamine – 2 (D_2) receptors in the mesolimbic and mesocortical dopaminergic tracts. These new medications differ from the conventional agents by demonstrating clinical efficacy while producing fewer extra-pyramidal symptoms (EPS); they are beneficial in treating negative symptoms and may also improve the neurocognitive deficits associated with schizophrenia. Their mechanism also differs from that of previously used drugs with greater affinity for antagonism of post-synaptic serotonin – 2 (5-HT_2) receptors and also greater than the affinity for antagonism of D_2 receptors. However, different side effects have been seen with individual agents, including weight gain and somnolence, which can decrease compliance and persistency, (Fleischhacker WW et al, 1999; Kurzthaler I et al, 2001) leading to increased relapse. Thus, there is still an unmet need for novel antipsychotic drugs that are better tolerated than earlier typical agents and currently available atypical medications. In addition, enhanced overall efficacy against the positive symptoms, negative symptoms, and cognitive dysfunction of schizophrenia remains an unmet medical need.

Aripiprazole is a novel agent with a unique pharmacologic profile that acts as a potent partial agonist at dopamine D_2 receptors, a partial agonist at serotonin 5-HT_{1A} receptors, and an antagonist at 5-HT_{2A} receptors. (Burris KD et al, 2002; Jordan S et al, 2002; McQuade RD et al, 2002). It has been suggested that dopamine partial agonists maybe capable of stabilizing the dopaminergic system without inducing the hypodopaminergia that limits the tolerability of currently available antipsychotics. (Carlsson A. et al, 2000; Stahl SM, 2001) Aripiprazole acts as a functional antagonist at D_2 receptors under hyperdopaminergic conditions, but exhibits functional agonist properties under hypodopaminergic conditions. In addition to dopamine D_2 partial agonism, aripiprazole acts as a partial agonist at some 5-HT receptor sub-types and as an antagonist at others. At 5-HT_{1A} receptors, aripiprazole is a partial agonist. (Jordan S et al, 2002) Putative relationships have also been postulated between 5-HT_{1A} agonism and improvement in depression, cognition and negative symptoms. (Millan MJ, 2000) Preclinical studies have demonstrated that aripiprazole is an antagonist at 5-HT_{2A} receptors. (McQuade RD, 2002) Antagonism at 5-HT_{2A} receptors may confer a favorable effect on negative symptoms (Millan MJ 2000; Leysen JE et al. 1993; Rao ML et al, 1994) and have an association with low EPS liability. (Richelson E,1999)

In combination, the above studies suggest that aripiprazole may function as a dopamine-serotonin system stabilizer, an agent that acts as a functional antagonist or functional agonist at dopamine and serotonin receptors depending on the level of the relevant neurotransmitters in the environment (Kane JM et al, 2002). The activity of aripiprazole at dopamine and serotonin receptors suggests that the drug may have overall efficacy against the symptoms of schizophrenia, including both positive and negative symptoms, with a low risk of side effects. This multicenter, randomized, open labeled post-marketing study was conducted to evaluate the efficacy and tolerability of aripiprazole for the treatment of Indian patients with acute relapse of schizophrenia or schizoaffective disorder.

Material & Method

Inclusion criteria

The clinical study required that participants were males and non-pregnant, non-lactating females using suitable contraceptive measures, aged 18 to 65 years, with a primary diagnosis of acute relapse of schizophrenia or schizoaffective disorder (DSM IV criteria). The diagnostic evaluation included the following: psychiatric evaluation (DSM IV) for the diagnosis of schizophrenia or schizoaffective disorder, history of the disease, and history of response to treatment, a general clinical evaluation (including medical history, physical examination, and current symptoms), medication history during past week, Positive And Negative Syndrome Scale (PANSS) (Kay SR et al, 1987) and the mean general psychopathology scores, demographics, as well as vital signs, body weight, electrocardiogram (ECG), and laboratory liver function tests.

Exclusion criteria

Patients were excluded from the study if they had a psychiatric disorder other than schizophrenia or schizoaffective disorder, history of violence, history of suicidal attempts or serious suicidal ideation, a clinically significant neurologic abnormality other than tardive dyskinesia or EPS, psychoactive drug abuse or dependence, drug or alcohol abuse, or treatment with an investigational drug within 4 weeks prior to washout phase. Patients were also excluded if they had any other acute or unstable medical condition. After complete description of the study to the subjects or caregiver, written informed consent was obtained.

Study Duration & Follow -up

This randomized, open labeled, multicentric, 4-week post-marketing study was conducted at 53 primary care centers in India over the time period of August 2003 to April 2004. Patients were screened for inclusion into the study at the initial visit. Additionally, at screening the following data were collected: demographics, clinical examination and prior antipsychotic use. Patients were enrolled as per the study inclusion criteria, provided they did not have any other psychiatric disorder nor a significant abnormal laboratory value, or any acute or unstable medical condition. Patients included in the study were given 15mg of aripiprazole once daily and treated for 4 weeks. At the end of 2 weeks, if the patients showed reduction in PANSS total score ≥30% then they were to continue treatment on same dosage. But, if PANSS total score reduction was <30% then dosage was to be increased to 30 mg once daily.

Patient Assessment

Clinical Efficacy

Treatment efficacy was assessed using the PANSS scale and changes in general psychopathology. The PANSS evaluation included the total score (30 items), the positive subscale (7 items), and the negative subscale (7 items). Symptom severity was rated using a 7-point scale. Then a general psychopathology was evaluated for each patient. Efficacy assessments were performed at screening (baseline), and at the end of two weeks and four weeks of treatment (days 14 and 28). The efficacy variable evaluated included the mean change from baseline to week 4 in PANSS total, PANSS positive and negative subscale & the mean changes in score of general psychopathology.

Safety evaluation

Adverse events were monitored at the time of intervention (Day 14) and at the end of the study medication. The status and intensity of the reported adverse events were also evaluated at the visit assessment. EPS were evaluated at baseline and visits during the study using the Simpson-Angus Scale (Simpson GM et al, 1970) and the Abnormal Involuntary Movement scale (AIMS) (Guy W, 1976). Vital signs were monitored at baseline and on days 14 and 28. Twelve – lead ECGs, blood samples, and urinalysis were assessed at baseline and at the end of therapy (at the discretion of the investigators).

Study medication

The patients enrolled were given aripiprazole (15mg) and use of psychotropic agents (other than study medication) was prohibited throughout the treatment period of the study, except for lorazepam for anxiety or insomnia or an intramuscular lorazepam given in cases of emerging agitation. Benztropine treatment was allowed for EPS, if judged necessary by the investigators.

Study Analysis

Analysis of efficacy parameters was performed on an intent-to-treat (ITT) basis using data obtained from each patient's last visit. The ITT population consisted of all patients with at least 1 baseline and post baseline evaluation. The efficacy parameters were evaluated by Analysis Of Variance (ANOVA). Analysis of the vital parameters was also evaluated by ANOVA. Statistical significance was reached if the p value was less than or equal to 0.05.

Results

Patients

In this study 249 patients were enrolled. Baseline characteristics for the randomized patients are listed in Table 1. Of the 249 randomized patients, 230 completed the 4-week study period (ITT). Reason for discontinuation of the remaining was that they lost to follow-up.

Table 1: **Baseline Demographic Characteristics, including efficacy & safety parameters (all patients)**

Characteristic	Aripiprazole, 15mg (n=249)
Male/female (N)	131/118
Age (18-60 yrs), Mean ± SE	33.61 ± 10.51
Body weight (kg) Mean ± SE	60.51 ± 11.42

Patients included in the study were evaluated for efficacy by assessing their baseline PANSS (total, positive, negative) and general psychopathology (Table 2).

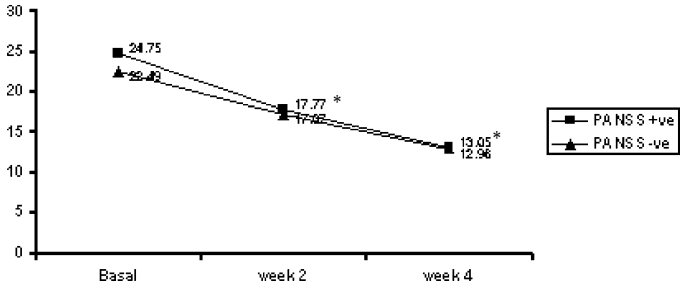
Table 2: **Clinical profile on administration**

Variables	Baseline (Mean±SE)
PANSS total score	92.63 ± 30.6
PANSS positive subscale score	24.75 ± 9.5
PANSS negative subscale score	22.49 ± 10.79
General psychopathology	45.49 ± 15.64

Efficacy Results

Aripiprazole doses produced significant improvement from

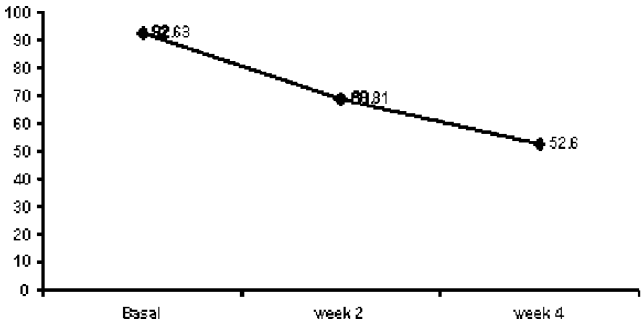
the baseline in the following measures: PANSS total score, PANSS positive subscale score, PANSS negative subscale score and general psychopathology. All treatment groups demonstrated similar efficacy.



* $p < 0.05$ significant

Figure 1: Comparative PANSS Score (Positive & negative)

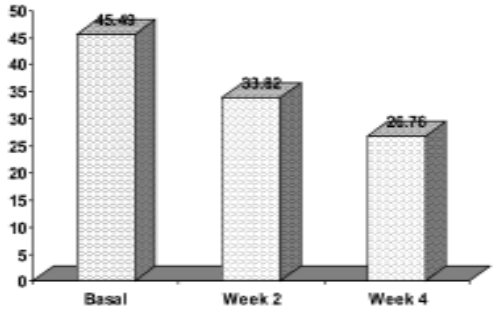
Average positive syndrome scale was 24.75 at baseline. After treatment at the end of 2nd week mean score had a significant reduction i.e. 28.8% and at the end of treatment it was 47.3%. The mean negative syndrome scale was 22.49 at baseline evaluation. After treatment the mean score had a reduction of 24.1% at 2nd week and 42.4% at the end of treatment, which were statistically significant (Figure 1).



* $p < 0.05$ significant

Figure 2: Total PANSS score as compared to baseline

The mean total PANSS score at the end of 2nd week had a reduction by 25.7% and 43.2% reduction at the end of treatment from baseline (92.63), which were statistically significant. (Fig. 2)



*$p < 0.05$ significant

Figure 3: Mean Scores of General Psychopathology

After treatment at the end of 2nd week the mean general psychopathology score had a reduction of 25.7% from baseline. At the end of treatment (week 4) reduction of 41.2% was observed from baseline, which was statistically significant. (Figure 3)

Safety

Adverse events

Aripiprazole treatment was well tolerated, with adverse events generally mild-to-moderate in intensity and not treatment- limiting. Overall, 19 (7 %) of the 249 randomized patients failed to follow-up for the study. The most frequent adverse events i.e. those occurring at an incidence of 5% or more in the treatment group was not seen throughout the study population. The incidences of the common side effects were tremors (4.8%), restlessness (3.6%), akathisia (3.2%), rigidity (2.8%), followed by 2% nausea/ vomiting, headache, EPS and flatulence (Table 3) No patients in the study group discontinued due to any of the adverse events. The overall incidence of EPS related adverse events in the study group were negligible.

Comparison of mean change in body weight in the study group demonstrated no significant differences from baseline evaluation. Also no significant changes in the QTc interval were observed. There was no clinically significant difference in vital signs or laboratory results in the study group.

Table 3: **Incidence of adverse events (< 5% in the study group)**

Adverse events	N (%)
Tremors	12 (4.8)
Rigidity	7 (2.8)
Restlessness	9 (3.6)
Akathisia	8 (3.2)
EPS	6 (2.4)
Nausea/vomiting	5 (2.0)
Flatulence	5 (2.0)

Discussion

The current study found that aripiprazole 15mg/day were effective, safe, and well tolerated for the treatment of patients with acute relapse of schizophrenia or schizoaffective disorder. Aripiprazole produced significant improvements compared with baseline for change in PANSS total, PANSS positive & negative subscales and general psychopathology scores. These efficacy data clearly indicate that aripiprazole is effective in treating the acute symptoms of schizophrenia. This data also further

demonstrates that a dopamine D_2 partial agonist can exhibit clinically meaningful and sustained improvements in schizophrenic symptoms, with sustained efficacy throughout the 4-week duration of the study.

Treatment with aripiprazole was well tolerated at the recommended doses. Adverse events were generally mild-to moderate across all treatment groups and tended not to be treatment limiting. Recent attention has been focused on weight gain as a side effect of certain antipsychotic drugs (Allison DB et al, 2001); weight gain due to antipsychotics has important implications for health with long-term use. In this study, a very modest mean increase in body weight over the 4-week study period (range 0.2-0.9 kg) that did not differ significantly from baseline was recorded. Prolonged QTc interval, an ECG abnormality that has been associated with certain antipsychotic drugs, produces a small but increased risk of potentially dangerous cardiac arrhythmias (Gury C et al, 2000). In the current study, mean change in the QTc was not statistically different from the baseline values. No patient in the study group receiving aripiprazole experienced a clinically meaningful change in QTc interval, further confirming as previous study (Kane JM et al, 2002) that aripiprazole does not carry the risk of potentially fatal ECG changes. Amongst the currently available antipsychotic drugs, the major undesirable side effect is to cause sedation, an effect that can negatively impact a patient's functioning and adherence with prescribed therapy, especially in long-term treatment. The incidence of sleep disturbance was minimal (0.4%). Extra pyramidal side effects have been long associated with antipsychotic drugs and have the potential to limit their tolerability and effectiveness. The overall profile of aripiprazole for parkinsonism, akathisia and dyskinesia was not significant throughout the study period. The low risk of EPS as observed in this study and other aripiprazole studies maybe explained by its partial agonism at D_2 receptors, in contrast to the D_2 antagonism of currently available antipsychotics.

The results of the present study indicate that aripiprazole has considerable potential for the treatment of psychotic disorders. The findings of the current study are consistent with the clinical effects predicted by aripiprazole's unique pharmacodynamic profile, which includes potent D_2 partial agonist activity combined with partial agonism at 5-HT_{1A} receptors and antagonism at 5-HT_{2A} receptors. These data also support the conclusion that aripiprazole is the first agent that is not a D_2 antagonist to demonstrate a rapid onset of action with sustained antipsychotic efficacy over 4 weeks. The antipsychotic effects of aripiprazole given once daily were achieved with excellent safety and tolerability profile, with no evidence of marked EPS, weight gain, QTc prolongation or sleep disturbances. These data suggest that aripiprazole provides atypical antipsychotic efficacy with minimal side effects and has the potential to lead to increased treatment adherence and decreased relapsed rates.

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