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Research report

The efficacy, safety, and tolerability of aripiprazole for the treatment of schizoaffective disorder: Results from a pooled analysis of a sub-population of subjects from two randomized, double-blind, placebo-controlled, pivotal trials

Ira D. Glick [a,*], Raymond Mankoski [b], James M. Eudicone [b], Ronald N. Marcus [c], Quynh-Van Tran [d], Sheila Assunção-Talbott [b]

[a] *Department of Psychiatry and Behavioral Sciences, and Psychopharmacology, Stanford University School of Medicine, Stanford, CA, USA*
[b] *Bristol-Myers Squibb, Plainsboro, NJ, USA*
[c] *Bristol-Myers Squibb, Wallingford, CT, USA*
[d] *Otsuka America Pharmaceutical, Inc. Rockville, MD, USA*

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Abstract

Background: Schizoaffective disorder shares clinical characteristics with schizophrenia and affective disorders, with patients experiencing concurrent manic, mixed, or depressive episodes during psychosis. Because efficacy may be better in schizoaffective disorder than schizophrenia, this *post-hoc* analysis examines the efficacy, safety, and tolerability of aripiprazole in patients with schizoaffective disorder.

Method: Data were obtained from a sub-sample of subjects with schizoaffective disorder (randomized: aripiprazole $n=123$, placebo $n=56$) who participated in two 4-week, multicenter, double-blind trials of subjects with schizophrenia or schizoaffective disorder. Aripiprazole was administered at fixed doses of 15 mg/day, 20 mg/day, or 30 mg/day. Efficacy assessments included the Positive and Negative Syndrome Scale (PANSS) Total score, and the Positive, Negative, and General Psychopathology subscale scores. Safety and tolerability evaluations included incidence of treatment-emergent adverse events and extrapyramidal symptom assessments (SAS, BARS, and AIMS), and metabolic profile changes including weight and BMI.

Results: A significantly greater improvement from baseline to endpoint was observed with aripiprazole compared with placebo on the PANSS Total (−15.9 vs. −3.4; $p=0.038$) and PANSS Positive subscale (−4.6 vs. −1.0; $p=0.027$). Differences between treatments were not significant for the PANSS Negative subscale score (−3.7 vs. −1.2; $p=0.15$) or PANSS General Psychopathology subscale score (−8.3 vs. −3.1; $p=0.06$). There were no statistically significant differences at endpoint between groups in the mean change from baseline to endpoint in weight, glucose, or total cholesterol, or on SAS, BARS, or AIMS scores. There was a statistically significant decrease in prolactin in subjects treated with aripiprazole compared with placebo (−5.6 vs. −1.3, $p<0.001$).

Conclusion: Aripiprazole was efficacious and well tolerated in patients with schizoaffective disorder.
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Keywords: Schizophrenia spectrum; Antipsychotic; Atypical

* Corresponding author. Tel.: +1 650 723 3519.
E-mail address: iraglick@stanford.edu (I.D. Glick).

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1. Introduction

Schizoaffective disorder is characterized by concurrent symptoms of schizophrenia and affective disorders. According to the DSM-IV-TR (APA, 2000), the essential feature of schizoaffective disorder is an uninterrupted period of illness during which, at some time, there is a major depressive, manic, or mixed episode concurrent with the symptoms that meet criteria for schizophrenia (e.g., delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms). According to the DSM-IV-TR, during the same period of illness, there must be delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms, and mood symptoms should be present for a substantial proportion of the period of illness (APA, 2000).

From epidemiologic, clinical, and prognostic perspectives, schizoaffective disorder can be conceptualized as part of a continuum of psychiatric illnesses, with schizophrenia and bipolar disorder at the severe opposite ends of the spectrum, and schizoaffective disorder in the middle (Crow, 1986; Benabarre et al., 2001). This concept is supported by long-term outcomes research (Harrow et al., 2000). For patients with schizoaffective disorder, clinical characteristics such as overall outcome, required medication, work functioning, and rehospitalization rates were shown to be better than those seen in patients with schizophrenia but worse than patients with psychotic affective disorders. Although patients with schizoaffective disorder may have some better outcomes than patients with schizophrenia, schizoaffective disorder is still profoundly debilitating and follows a lifelong course punctuated by acute relapses that may often require hospitalization (Marneros, 2003). Up to two-thirds of patients with schizoaffective disorder show suicidal symptomatology at least once during the long-term course of the illness (Marneros, 2003). Epidemiologically, this disorder is relatively common. For example, it has been estimated that the prevalence of schizoaffective disorder among clinical populations may be as high as 16±12% (range 2–29%) (Keck et al., 1994).

Pharmacologic treatment of schizoaffective disorder may involve a combination of antipsychotics, antidepressants, or anti-manic agents, depending on the patient's symptom history and current status. A recent review of hospitalized patients with schizoaffective disorder showed an increase in the use of divalproex and atypical antipsychotics and a decline in the use of lithium and typical antipsychotics (Flynn et al., 2002). This increase in the use of atypicals is driven by expanding data on the efficacy and safety of these agents in a range of psychiatric disorders. For example, in addition to their established efficacy to treat the positive and negative symptoms of schizophrenia (Davis et al., 2003), some atypical antipsychotic agents are also effective for the treatment of mood disorders, such as bipolar disorder (Keck et al., 2003b; Hirschfeld et al., 2004; Tohen et al., 2003; Calabrese et al., 2005) and major depressive disorder (Berman et al., 2007, Marcus et al., 2008). These findings support the use of atypicals in the treatment of disorders that have both a psychotic component and an affective component, and atypical antipsychotics may be considered as a first-line treatment for patients with schizoaffective disorder (McElroy et al., 1999), which has both aspects.

Aripiprazole is a novel atypical antipsychotic which, unlike other antipsychotics in this class, is a partial dopamine D_2 receptor agonist (Burris et al., 2002) as opposed to a full dopamine antagonist. As a partial agonist, aripiprazole acts as a functional antagonist in conditions of high dopamine concentrations and a functional agonist in conditions of low dopamine concentration. The latter property is particularly important because prevention of hypodopaminergic levels in the nigro-striatal dopamine pathway is associated with lower risk for Parkinson-like symptoms that can result from complete D_2 antagonism. In addition, aripiprazole shows partial agonist activity at serotonin 5-HT_{1A} receptors (Jordan et al., 2002). These receptors are linked to improvements in the negative, cognitive, and depressive symptoms of schizophrenia (Millan, 2000), and their activation may also impart anxiolytic effects (Glennon and Dukat, 1995). Aripiprazole also has antagonist activity at serotonin 5-HT_{2A} receptors (Jordan et al., 2004). Antagonism of these receptors has been associated with improvement in the negative symptoms of schizophrenia (Leysen et al., 1993; Rao and Moller, 1994).

The efficacy, safety, and tolerability of aripiprazole have been shown in short-term and long-term clinical trials of patients with schizophrenia and bipolar I disorder, and as adjunctive treatment in major depressive disorder (Berman et al., 2007; Kane et al., 2002; Kasper et al., 2003; Pigott et al., 2003; Potkin et al., 2003; Kern et al., 2006; Kane et al., 2007; McEvoy et al., 2007; Keck et al., 2003a; Marder et al., 2003; Vieta et al., 2005; Keck et al., 2006; Sachs et al., 2006; Keck et al., 2007). For these reasons, it is expected that a similar clinical profile would be apparent in patients with schizoaffective disorder. Because efficacy may be better in schizoaffective disorder than schizophrenia, this analysis assessed the efficacy, safety and tolerability

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