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Effects of aripiprazole once-monthly on domains of personal and social performance: Results from 2 multicenter, randomized, double-blind studies

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ABSTRACT

Objective: To assess the effects of maintenance therapy with aripiprazole once-monthly 400 mg on personal and social functioning.
Methods: Data were analyzed from 2 randomized, double-blind trials of patients with schizophrenia requiring chronic antipsychotic treatment. One study was a 52-week trial of aripiprazole once-monthly 400 mg versus placebo; the other was a 38-week trial of aripiprazole once-monthly 400 mg, oral aripiprazole (10–30 mg daily), and aripiprazole once-monthly 50 mg (subtherapeutic dose to test assay sensitivity). Functioning was assessed using the Personal and Social Performance (PSP) scale, comprising 4 domain subscales.
Results: In the 52-week study, 403 patients stabilized on aripiprazole once-monthly 400 mg were randomized to receive aripiprazole once-monthly 400 mg (n = 269) or placebo (n = 134). In the 38-week study, 662 patients stabilized on oral aripiprazole were randomized to receive aripiprazole once-monthly 400 mg (n = 265), oral aripiprazole (n = 266), or aripiprazole once-monthly 50 mg (subtherapeutic dose; n = 131). In the 52-week study, mean changes from baseline were significantly worsened with placebo compared with aripiprazole once-monthly 400 mg for PSP total score ($P < 0.001$) and domain scores for Personal and Social Relationships ($P < 0.001$), Self-Care ($P < 0.01$), and Disturbing and Aggressive Behavior ($P < 0.0001$). In the 38-week study, mean changes from baseline were significantly worsened with aripiprazole once-monthly 50 mg compared with aripiprazole once-monthly 400 mg for PSP total score ($P < 0.05$) and the Personal and Social Relationships domain score ($P < 0.05$).
Conclusion: Patient functioning, assessed using the PSP scale, was maintained in stabilized patients treated with aripiprazole once-monthly in 2 pivotal relapse studies.

1. Introduction

Schizophrenia is a severe, chronic, and for most patients, progressive disease, and a fundamental goal of long-term maintenance therapy is to optimize patient functioning and quality of life (Hasan et al., 2013). A key component of maintaining patient functionality is relapse prevention (Harvey et al., 2013), which may also reduce the associated socioeconomic burden of the disease (Awad and Voruganti, 2008; Hong et al., 2009; Karve et al., 2012).Recent international treatment guidelines recommend continuous antipsychotic treatment for relapse prevention (Buchanan et al., 2010; Kreyenbuhl et al., 2010; Hasan et al., 2013). Long-acting injectable (LAI) formulations of antipsychotics are valuable treatment alternatives to oral formulations for facilitating relapse prevention because of their potential to facilitate adherence monitoring (Hasan et al., 2013; Rauch and Fleischhacker, 2013).

Aripiprazole once-monthly, an extended-release injectable suspension for intramuscular use, is the first dopamine partial agonist available as an LAI. Aripiprazole once-monthly is approved for the treatment of schizophrenia. In a 52-week, randomized, double-blind trial, aripiprazole

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once-monthly 400 mg (with an option to reduce to 300 mg) significantly delayed time to impending relapse compared with placebo (Kane et al., 2012). In a subsequent 38-week, randomized, double-blind trial with rate of impending relapse as the primary endpoint, aripiprazole once-monthly 400 mg (with an option to reduce to 300 mg) was noninferior to oral aripiprazole 10 to 30 mg and more effective than a subtherapeutic 50-mg dose of aripiprazole once-monthly used to test assay sensitivity (Fleischhacker et al., 2014). The safety and tolerability profile of aripiprazole once-monthly 400 mg was similar in both studies (Kane et al., 2012; Fleischhacker et al., 2014) and consistent with that reported for oral aripiprazole in previous registrational maintenance studies (Kasper et al., 2003; Pigott et al., 2003).

Although patients in both aripiprazole once-monthly 400 mg studies also demonstrated symptomatic improvement (Kane et al., 2012; Fleischhacker et al., 2014), symptomatic improvements are not always associated with functional improvements in patients with schizophrenia (Tandon et al., 2010; Harvey et al., 2012; Karow et al., 2012; Wunderink et al., 2013). To further characterize the efficacy of aripiprazole once-monthly 400 mg for the treatment of schizophrenia, we assessed, and are reporting for the first time, personal and social functioning in the 52-week (Kane et al., 2012) and 38-week studies (Fleischhacker et al., 2014) using the Personal and Social Performance (PSP) scale (Morosini et al., 2000). Furthermore, we evaluated both total and PSP domain scores.

2. Methods

2.1. Patients and study designs

Data were analyzed from a 52-week, multicenter, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov Identifier, NCT00705783) (Kane et al., 2012) and a 38-week, multicenter, randomized, double-blind, active-controlled trial (ClinicalTrials.gov Identifier, NCT00706654) (Fleischhacker et al., 2014). The trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, the protocols were reviewed by the institutional review board at each center, any potential adverse events were fully explained to patients, and all patients provided written informed consent.

Study designs were previously described in detail (Kane et al., 2012; Fleischhacker et al., 2014). In brief, the 52-week study consisted of a screening phase, an oral conversion phase (4–6 weeks), an oral stabilization phase (4–12 weeks), an aripiprazole once-monthly stabilization phase (12–36 weeks), and a double-blind, placebo-controlled phase (52 weeks). During the aripiprazole once-monthly stabilization phase, patients were permitted, if required based on tolerability, a single decrease to 300 mg and a single return to 400 mg. Patients who met stability criteria were randomized to double-blind treatment (2:1) with aripiprazole once-monthly 400 mg or placebo. The primary efficacy endpoint was the time to impending relapse. Based on a prespecified interim analysis (performed after 64 events), an independent data monitoring committee concluded that the primary endpoint had been met, with no safety issues of particular concern, resulting in early termination of the 52-week study to avoid continued exposure to placebo.

The 38-week study comprised a screening phase, an oral conversion phase (4–6 weeks), an oral stabilization phase (8–28 weeks), and a double-blind maintenance phase (38 weeks). During the double-blind maintenance phase, patients who met stability criteria were randomly assigned (2:2:1) to treatment with aripiprazole once-monthly 400 mg, oral aripiprazole 10 to 30 mg daily (based on stabilization dose), or aripiprazole once-monthly 50 mg (low dose included to test assay sensitivity for the noninferiority design). Patients initiated on aripiprazole once-monthly 400 mg or 50 mg were allowed a one-time dose reduction to 300 mg or 25 mg, respectively, as well as a one-time return to the original dose. The primary efficacy endpoint was the estimated proportion of patients experiencing impending relapse by the end of 26 weeks from randomization to the double-blind maintenance phase.

Patient inclusion and exclusion criteria were previously described in detail (Kane et al., 2012; Fleischhacker et al., 2014). In brief, eligible patients were 18 to 60 years of age with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (*DSM-IV-TR*™) diagnosis of schizophrenia for ≥3 years before screening who were considered by the investigators to require chronic antipsychotic treatment.

2.2. Assessment of personal and social functioning

Personal and social functioning were measured using the 100-point PSP scale, a validated clinician-rated scale that measures personal and social functioning across 4 domains: (1) Socially Useful Activities, Including Work and Study, (2) Personal and Social Relationships, (3) Self-Care, and (4) Disturbing and Aggressive Behaviors (Morosini et al., 2000). Impairment in each domain was rated on a 6-point scale (0 = absent, 1 = mild, 2 = manifest, 3 = marked, 4 = severe, and 5 = very severe). PSP total score ratings were converted to a 0- to 100-point total score (71–100, mild functional difficulty; 31–70, varying degrees of disability; 1–30, minimal functioning needing intense support and/or supervision) using algorithms to identify the appropriate 10-point interval within the 100-point range and using the rater's judgment to determine the total score within the 10-point interval. To provide additional insight into the domains of PSP, we report actual baseline mean domain scores and mean change scores based on actual investigator ratings, where decreasing scores indicate improved function.

2.3. Statistical analyses

In the 52-week study, PSP total score was assessed at baseline and week 12/last visit of the oral stabilization phase, week 36/last visit of the aripiprazole once-monthly stabilization phase, and week 52/last visit of the double-blind, placebo-controlled phase. The value at the end of the aripiprazole once-monthly stabilization phase, on the day of randomization before the first dose of double-blind medication, served as the baseline for the double-blind, placebo-controlled phase. Change from baseline to week 52/last visit in PSP total score during the double-blind, placebo-controlled phase was analyzed using analysis of covariance (ANCOVA; last observation carried forward [LOCF]), with treatment as a factor and baseline value as a covariate.

In the 38-week study, PSP total score was assessed at baseline and week 28/last visit of the oral stabilization phase, and week 38/last visit of the double-blind maintenance phase. Change from baseline in PSP total score during the double-blind maintenance phase was analyzed using ANCOVA (LOCF), with treatment as a factor and baseline value as a covariate.

As with PSP total score, changes from baseline in PSP domain scores during the double-blind phases of both studies were analyzed post-hoc using ANCOVA (LOCF), with treatment as a factor and baseline value as a covariate.

Additional post-hoc subgroup analyses evaluated change from baseline in PSP total and domain scores during the double-blind phases of both studies in the subgroup of patients with impending relapse, as defined in the primary publications (Kane et al., 2012; Fleischhacker et al., 2014). These analyses used ANCOVA (LOCF), with treatment as a factor and baseline value as a covariate.

3. Results

3.1. Patient disposition and characteristics

Patient disposition and demographics were detailed in the primary study publications (Kane et al., 2012; Fleischhacker et al., 2014). In the 52-week study, 1025 patients were screened, 843 were enrolled, and 403 entered the double-blind, placebo-controlled phase (aripiprazole