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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

once-monthly, n = 269; placebo, n = 134). Because the study was terminated early, 51 (8.9%) patients received at least 12 months (13 injections) of aripiprazole once-monthly 400 mg treatment during the aripiprazole once-monthly 400 mg stabilization and double-blind, placebo-controlled phases. Baseline demographic and disease characteristics were similar between groups. Mean (SD) age was 40.6 (10.8) years. The majority of patients were men (59.8%) and white (60.5%). Mean (SD) age at first diagnosis was 26.0 (8.5) years.

In the 38-week study, 1118 patients were screened, 937 were enrolled, 662 were randomized to double-blind treatment (aripiprazole once-monthly 400 mg, n = 265; oral aripiprazole, n = 266; aripiprazole once-monthly 50 mg, n = 131), and 435 (65.7%) completed 38 weeks of treatment. Baseline demographic and disease characteristics were similar between treatment groups. Mean (SD) age was 41.2 (10.4) years, 61.3% of patients were men, and 58.5% were white. Mean (SD) age at first diagnosis was 27.3 (9.0).

3.2. Personal and social functioning

3.2.1. PSP total score

In the 52-week study, mean (SD) PSP total score was 62.7 (14.1) (i.e., varying degrees of disability) at the beginning of the oral stabilization phase. Mean PSP total scores increased from baseline to last visit of the oral stabilization phase (indicative of improvement) and from baseline to last visit of the aripiprazole once-monthly stabilization phase. During the double-blind, placebo-controlled phase, change from baseline in PSP total scores was significantly greater at week 52 with placebo compared with aripiprazole once-monthly 400 mg, indicating greater functional deterioration with placebo ($P < 0.001$; Fig. 1A).

In the 38-week study, mean (SD) PSP total score was 63.3 (12.6) at the beginning of the oral stabilization phase and was increased at the final visit. During the double-blind maintenance phase, PSP total scores remained fairly stable in the aripiprazole once-monthly 400 mg and oral aripiprazole groups but decreased in the aripiprazole once-monthly 50 mg group; there was no difference between aripiprazole once-monthly 400 mg and oral aripiprazole (Fig. 1B). Mean change from baseline in PSP total score at week 38 was significantly greater with aripiprazole once-monthly 50 mg compared with aripiprazole once-monthly 400 mg and oral aripiprazole, indicating greater functional deterioration with aripiprazole once-monthly 50 mg ($P < 0.05$; Fig. 1B).

3.2.2. PSP domain scores

Changes from baseline in actual mean PSP domain scores during the double-blind, placebo-controlled phase of the 52-week study are plotted in Fig. 2A. Across groups, mean PSP domain scores at randomization were all less than 2, indicating no greater than mild impairment. PSP domain scores increased slightly (≤0.5 points on the 6-point domain score scale) in both groups during the double-blind, placebo-controlled phase, indicative of worsening, but remained below 2. Mean change from baseline in Socially Useful Activities domain score at week 52 was not significantly different between treatment groups, whereas there was a significant difference between placebo and aripiprazole once-monthly 400 mg for the domains of Personal and Social Relationships, Self-Care, and Disturbing and Aggressive Behaviors ($P < 0.001$, $P < 0.01$, and $P < 0.0001$, respectively), indicating greater functional deterioration with placebo.

Changes from baseline in mean PSP domain scores during the double-blind maintenance phase of the 38-week study are plotted in Fig. 2B. Across groups, mean PSP domain scores at week 38 were all less than 2, indicating no greater than mild impairment. At week 38, mean change from baseline in the Personal and Social Relationships domain score was significantly greater with aripiprazole once-monthly 50 mg compared with aripiprazole once-monthly 400 mg and oral aripiprazole ($P < 0.05$), indicating greater deterioration with aripiprazole once-monthly 50 mg. There was no difference between aripiprazole once-monthly 400 mg and oral aripiprazole. Significant differences between groups were not observed for the other domain scores at week 38.

3.2.3. PSP scores in patients with impending relapse

In the subgroup of patients with impending relapse in the 52-week study, the mean (SD) double-blind, placebo-controlled baseline PSP total score was 65.5 (12.27) with aripiprazole once-monthly 400 mg (n = 27) and 65.1 (11.3) with placebo (n = 49). The mean (SD) change from baseline in PSP total score at week 52 was −16.0 (14.8) and −12.9 (10.8), respectively.

In the subgroup of patients with impending relapse in the 38-week study, the mean (SD) double-blind baseline PSP total score was 62.3 (12.2) with aripiprazole once-monthly 400 mg (n = 22), 63.2 (9.6) with oral aripiprazole (n = 19), and 64.0 (11.2) with aripiprazole once-monthly 50 mg (n = 29). The mean (SD) change from baseline in PSP total score at week 38 was −14.4 (16.7), −11.0 (14.0), and −9.3 (9.7), respectively.

4. Discussion

These results from 2 long-term, randomized, double-blind trials demonstrate that patient personal and social functioning, assessed using the PSP scale, improved during the oral and aripiprazole once-monthly 400 mg stabilization phases (52-week study) and was maintained in stabilized patients randomized to continue treatment with aripiprazole once-monthly 400 mg, compared with worsening in those receiving placebo (52-week study) or a subtherapeutic dose of aripiprazole once-monthly (38-week study). Changes on individual domain scores were generally consistent with the PSP total change score, providing further evidence that patient functioning was maintained in patients treated with aripiprazole once-monthly 400 mg maintenance therapy. The individual domain data show what the PSP is measuring and what aspects of personal and social functioning are improving. In the 38-week study, there were no significant differences between aripiprazole once-monthly 400 mg and oral aripiprazole on the PSP total or individual domain scores, as may be expected in a randomized, controlled trial, where adherence is fostered through regular study visits.

Our results are generally consistent with a similarly designed relapse prevention study for the LAI paliperidone palmitate, in which improvements in functioning were observed in the stabilization phases and maintained in the double-blind phase for the active treatment group, with worsening in patients randomized to placebo (Hough et al., 2010). In comparison, in a study examining switching from oral antipsychotics to paliperidone palmitate and risperidone LAIs, patient functioning was lower at baseline and showed a greater change from baseline in the first 3 months after the switch (Alphs et al., 2013). It appears that patient functioning is maintained during long-term relapse prevention trials in which patients have less severe impairment at baseline. However, compared with relapse prevention studies, where patients are stable at randomization, studies in patients with acute exacerbations of schizophrenia generally show larger effect sizes for PSP scores (Kane et al., accepted for publication; Sliwa et al., 2011).

The exploratory analysis of PSP scores in patients with impending relapse showed substantial functional deterioration accompanying relapse. The importance of symptom control in preserving function in patients with schizophrenia is established (Haynes et al., 2012; Helldin et al., 2007). However, there is only partial congruence between symptom control and functional status (Karow et al., 2012; Wunderink et al., 2013), which may be partly related to the sensitivity of functional scales as well as to disease progression despite use of antipsychotic agents (Tandon et al., 2010). The impact of antipsychotic treatment on functional status is still not clear (Tandon et al., 2010). With the potential of LAIs to improve adherence, further studies on the effects of LAIs on patient function are needed. More information on the temporal relationship between functional decline and impending relapse

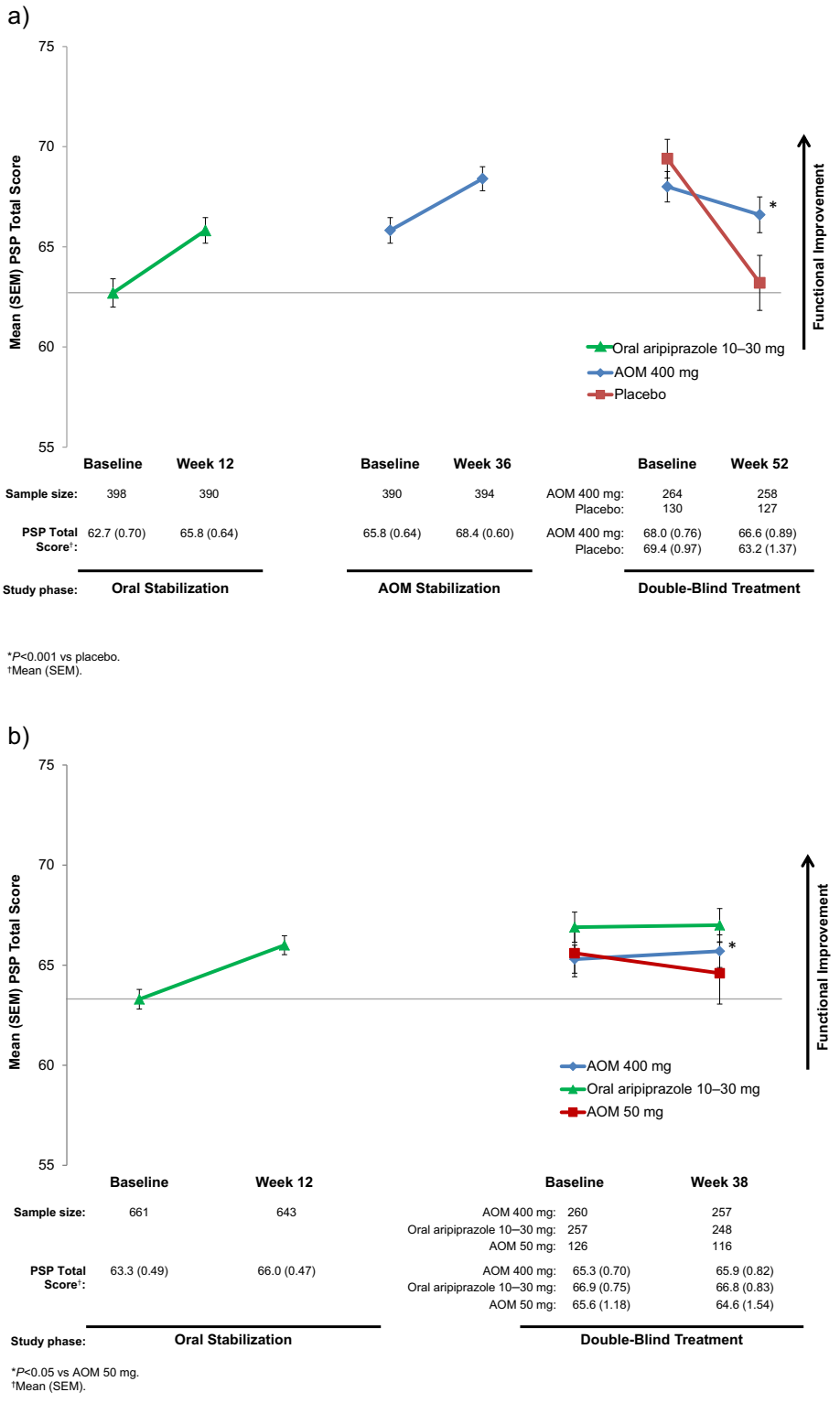

Fig. 1. Change from baseline in PSP total score (LOCF) during (A) the oral stabilization, aripiprazole once-monthly stabilization, and double-blind placebo-controlled phases of the 52-week study and (B) the oral stabilization and double-blind maintenance phases of the 38-week study. Increase in scores indicates improvement of functioning. For the aripiprazole once-monthly stabilization (52-week study) and double-blind (both studies) phases, baseline is the value at the end of the preceding phase. AOM = aripiprazole once-monthly; LOCF = last observation carried forward; PSP = Personal and Social Performance; SEM = standard error of the mean.

(i.e., whether functional decline precedes symptom deterioration or whether re-emergence of symptoms leads to functional decline) may help clinicians identify patients at risk of relapse before full relapse.

There are several limitations to the present analyses. Both studies were designed to evaluate patient relapse, and all patients were stabilized on oral aripiprazole or aripiprazole once-monthly before randomization to double-blind treatment. During all stabilization phases of both studies, PSP total scores improved. As such, the study designs may have precluded the ability to observe robust improvements in PSP scores during the double-blind study phases. Also, patients were mildly symptomatic at study entry (based on Positive and Negative Syndrome Scale [PANSS] scores), which may limit the generalizability of

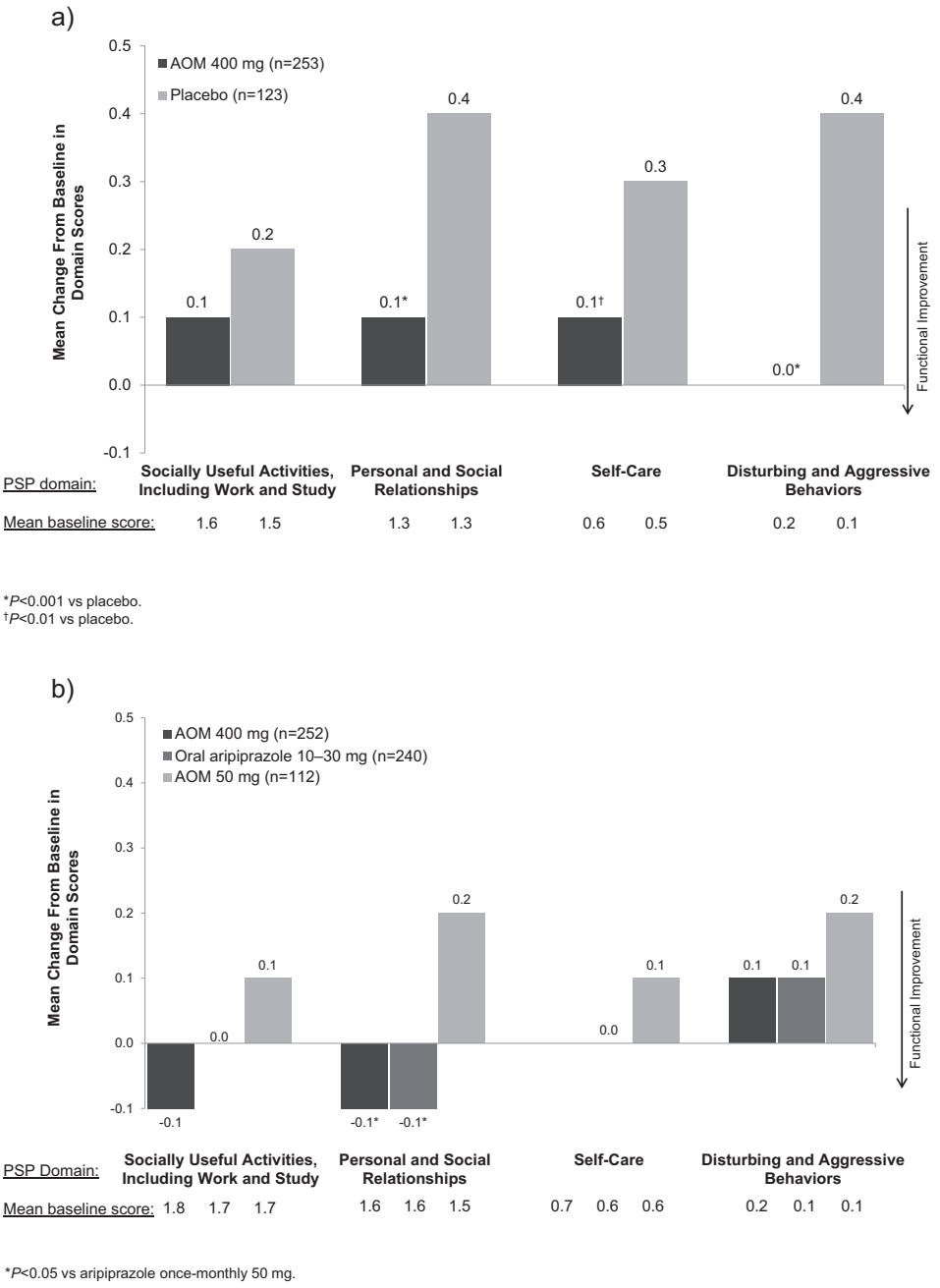

Fig. 2. PSP domain scores (LOCF) during the double-blind placebo-controlled phase of (A) the 52-week study and (B) the 38-week study for Socially Useful Activities, Including Work and Study; Personal and Social Relationships; Self-Care; and Disturbing and Aggressive Behaviors. Reduction in scores indicates improvement of functioning. Data were analyzed post-hoc. AOM = aripiprazole once-monthly; LOCF = last observation carried forward; PSP = Personal and Social Performance.

our findings. Data from studies of aripiprazole once-monthly 400 mg in the treatment of acute schizophrenia may help resolve questions related to the study design limitations.

The geographic heterogeneity of the patients included in the analysis (i.e., the 52-week and 38-week studies included patients from 12 and 14 countries, respectively) is a strength with regard to global applicability; however, it is also a limitation because some aspects of personal and social function may vary based on geoeconomic status. It should also be noted that the early termination of the 52-week study prevented patients from receiving aripiprazole once-monthly 400 mg for all 52 weeks of the double-blind period (Kane et al., 2012).

In conclusion, aripiprazole once-monthly 400 mg maintained stability in personal and social functioning achieved early in treatment. Assessed using the PSP scale, functional outcomes deteriorated with placebo or a subtherapeutic dose of aripiprazole once-monthly (50 mg). Further studies are warranted to better understand the association between antipsychotic treatment and functional status, particularly the relationship between functional decline and relapse.

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Contributors

W. Wolfgang Fleischhacker, John M. Kane, Robert D. McQuade, Brian R. Johnson, Pamela P. Perry, William H. Carson, and Raymond Sanchez were involved in conception and design of the studies. Timothy Peters-Strickland oversaw data analysis and reporting. Statistical analyses were conducted by Lan-Feng Tsai. Brian R. Johnson and Pamela P. Perry

led the execution of the trial. W. Wolfgang Fleischhacker provided patients for the trials. All authors were involved in manuscript development, critically reviewed the manuscript for important intellectual content, and approved the final version.

Conflicts of interest

W. Wolfgang Fleischhacker has received research grants from Otsuka, Pfizer, Janssen, and Reckitt-Benckiser, as well as consulting honoraria from Lundbeck, Roche, Bristol-Myers Squibb, Otsuka, Janssen, Pfizer, MedAvante, Takeda, Endo, and Vanda. He has received speaker honoraria from Lundbeck, Janssen, Otsuka, Roche, and Takeda. He holds stock from MedAvante.

Ross A. Baker, Raymond Sanchez, Lan-Feng Tsai, Timothy Peters-Strickland, Pamela P. Perry, Robert D. McQuade, William H. Carson, and Brian R. Johnson are employees of Otsuka Pharmaceutical Development & Commercialization, Inc.

Anna Eramo is an employee of Lundbeck LLC.

John M. Kane has received honoraria for lectures and/or consulting from Alkermes, Amgen, Bristol-Myers Squibb, Cephalon, Eisai, Boehringer Ingelheim, Eli Lilly, Forrest, Genentech, Intracellular Therapeutics, Janssen, Johnson & Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Pierre Fabre, Proteus, Reviva, Roche, Sunovion, and Targacept. He is a shareholder of MedAvante.

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