Journal of Affective Disorders 162 (2014) 20–25

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Effect of symptom severity on efficacy and safety of aripiprazole adjunctive to antidepressant monotherapy in major depressive disorder: A pooled analysis

Thomas D. Stewart [a], Ainslie Hatch [b], Kimberly Largay [c], John J. Sheehan [d,1], Sabrina V. Marler [e,1], Robert M. Berman [a,e,1], J. Craig Nelson [f,*]

[a] Yale School of Medicine, New Haven, CT, USA
[b] Otsuka America Pharmaceutical, Inc., Princeton, NJ, USA
[c] Otsuka Pharmaceutical Development and Commercialization, Princeton, NJ, USA
[d] Bristol-Myers Squibb, Plainsboro, NJ, USA
[e] Bristol-Myers Squibb, Wallingford, CT, USA
[f] Department of Psychiatry, University of California, San Francisco, 401 Parnassus Avenue, San Francisco, CA 94143, USA

ARTICLE INFO

Article history:
Received 28 February 2014
Accepted 7 March 2014
Available online 24 March 2014

Keywords:
Antidepressant therapy
Augmentation
Major depressive disorder
Symptom severity

ABSTRACT

Background: There is a paucity of evidence for outcome predictors in patients with major depressive disorder (MDD) not responding to initial antidepressant therapy (ADT). This post-hoc analysis evaluated whether MDD severity affects response to adjunctive aripiprazole.

Methods: Data from 3 randomized, double-blind, placebo-controlled trials of adjunctive aripiprazole in adults with MDD and inadequate response to 1 to 3 ADT trials were pooled and stratified based on Montgomery–Åsberg Depression Rating Scale (MADRS) total score (mild, ≤ 24; moderate, 25–30; severe, ≥ 31). Treatment differences in change in MADRS total score and rates of response ($\geq 50\%$ MADRS improvement) and remission (response with MADRS total score ≤ 10) were analyzed at endpoint. Adverse events were assessed within each subgroup.

Results: Aripiprazole produced greater improvement than placebo in the MADRS total score regardless of MDD severity at baseline (between-treatment difference [95% CI]: mild, −2.5 [−4.0 to −1.1]; moderate, −3.2 [−4.9 to −1.6]; severe, −4.5 [−6.8 to −2.2]). Compared with placebo, adjunctive aripiprazole increased the likelihood of response in all subgroups (risk ratio [95% CI]: mild, 1.50 [1.15, 1.95]; moderate, 1.51 [1.09, 2.11]; severe, 1.95 [1.23, 3.10]). Common treatment-emergent adverse events included akathisia and restlessness.

Limitations: The original studies were not designed to assess the efficacy of adjunctive aripiprazole by baseline severity, and this post-hoc analysis was not powered to evaluate differences in severity subgroups.

Conclusions: In patients who failed to respond to initial ADT, adjunctive aripiprazole was more effective than placebo in mild, moderate, and severe MDD strata.

Clinical trial registration: ClinicalTrial.gov: NCT00095823, NCT00105196, and NCT00095758.

1. Introduction

Major depressive disorder (MDD) is a common, burdensome, and often recurrent illness affecting an estimated 340 million people worldwide (Greden, 2001). Nonresponse to antidepressant therapy (ADT) is a frequent occurrence in clinical practice and a major public health challenge, with up to 60% of patients not achieving adequate response following ADT (Fava, 2003). The 2010 American Psychiatric Association (APA) guidelines for the treatment of depression recommend a change in treatment after four to eight weeks if there is inadequate response to the initial antidepressant (American Psychiatric Association, 2010). The change in treatment could include altering medication dose, switching medications, or augmentation therapy.

Ideally, selection of the next step in treatment would be based on predictors of outcome with various strategies. Unfortunately, evidence for predictors of outcome is limited. The large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study identified predictors of remission but did not address what factors

* Corresponding author. Tel.: +1 415 476 7405; fax: +1 415 476 7320.
E-mail address: CraigN@lppi.ucsf.edu (J.C. Nelson).
[1] At the time of the study.

http://dx.doi.org/10.1016/j.jad.2014.03.017
0165-0327/

predict differential response to individual treatments (Trivedi et al., 2006). Some guidelines have suggested that adjunctive strategies might be especially useful in partial responders (American Psychiatric Association, 2010); however, this is based on the practical aim of maintaining improvement rather than on evidence of efficacy. In fact, aripiprazole appears to be quite effective in nonresponders to initial treatment (Nelson et al., 2012).

The APA guidelines describe research into predictors of benefit and adverse events (AEs) as an important area of focus, and state that severity might be a predictor of outcome. In fact, the American Psychiatric Association guidelines recommend that depression severity be considered as a factor when selecting treatment (American Psychiatric Association, 2010). However, the guidelines are unclear about how severity might guide treatment other than advising that somatic treatments should be considered in severe patients (as opposed to psychotherapy alone). The lack of guidance here is again the result of limited evidence. A few reports suggest that antidepressants produce greater improvement in more severely depressed patients (Fournier et al., 2010; Khan et al., 2002; Kirsch et al., 2008); however, it is unclear whether this applies to adjunctive interventions.

Because of the lack of evidence regarding the predictive value of severity for next-step treatments, we undertook a post-hoc study using pooled data from three large, similarly designed double-blind clinical trials that demonstrated the efficacy of adjunctive aripiprazole for the treatment of MDD (Berman et al., 2007, 2009; Marcus et al., 2008). Our objective was to evaluate whether depression severity affects the response to adjunctive aripiprazole. Our hypothesis was that adjunctive aripiprazole would be more effective in severely depressed patients.

2. Methods

2.1. Study design

Data were pooled from three similarly designed studies assessing the efficacy and safety of aripiprazole adjunctive to ADT for the treatment of MDD. Details of the study designs were published previously (Berman et al., 2007, 2009; Marcus et al., 2008). The studies comprised three phases: a screening phase (Phase A, 7–28 days) during which prohibited medications were discontinued; an 8-week prospective phase (Phase B), in which patients received a selective serotonin reuptake inhibitor (SSRI) or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine extended release (XR) along with a placebo; and a 6-week randomized, double-blind phase (Phase C) during which patients with inadequate response received either adjunctive aripiprazole or placebo. The antidepressants initiated in Phase B were selected by the investigator and included escitalopram (10 or 20 mg/day), fluoxetine (20 or 40 mg/day), paroxetine controlled-release (37.5 or 50 mg/day), sertraline (100 or 150 mg/day), and venlafaxine XR (150 or 225 mg/day). Inadequate response was defined as a $<50\%$ reduction in the 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score from baseline to the end of Phase B, HAM-D-17 total score ≥ 14, and Clinical Global Impressions-Improvement (CGI-I) score ≥ 3 at weeks 6 and 8.

The studies were conducted in accordance with the Declaration of Helsinki; the ethics committee at each site approved the protocol. All participants provided written consent.

2.2. Patients

Eligible patients were aged 18 to 65 years and had an MDD diagnosis (Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition [DSM-IV-TR] criteria lasting ≥ 8 weeks and a HAM-D-17 total score ≥ 18). Patients had to report an inadequate response to 1 to 3 adequate ADT trials of ≥ 6-week duration at or above the minimum dose specified in the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.

2.3. Statistical analyses

For this post-hoc analysis, patients were stratified at the beginning of Phase C into 3 groups: mild (Montgomery–Åsberg Depression Rating Scale [MADRS] total score ≤ 24), moderate (MADRS total score 25–30), and severe (MADRS total score ≥ 31). A MADRS total score of ≥ 31 was previously found to best distinguish moderate and severe depression (Muller et al., 2003), and a cutoff of ≥ 30 has been used in several prior studies (Bose et al., 2012; Kennedy et al., 2009; Papakostas et al., 2012). However, the definition of mild versus moderate depression using the MADRS is not well established; therefore, definitions for mild and moderate depression in the current study were adapted from previous research (Kearns et al., 1982).

Adjusted mean change from Phase C baseline in MADRS total score, CGI-Severity (CGI-S) score, and CGI-I score for adjunctive aripiprazole and adjunctive placebo at 6 weeks was assessed using last observation carried forward (LOCF) and an analysis of covariance (ANCOVA) model, with double-blind treatment and study as main effects and end of Phase B assessment as the covariate for each category of baseline MADRS total score severity; results are reported as between-group differences with 95% CIs. Rates of response, defined as $\geq 50\%$ improvement from baseline to endpoint in MADRS total score, and remission, defined as MADRS total score ≤ 10 at the end of Phase C (LOCF), for adjunctive aripiprazole versus adjunctive placebo were analyzed using a Cochran–Mantel–Haenszel test, controlling for study and reported with 95% CIs. A Breslow–Day test was used to test for homogeneity of the odds ratios. To further assess the association between baseline severity and outcome on the MADRS, a univariate logistic regression model was used to examine the interaction of baseline severity as a continuous variable with the drug-placebo difference in outcome (LOCF).

Because this subgroup analysis is limited by its exploratory post-hoc nature, including reduced power, increased variance, and an increased influence of chance (Sleight, 2000), 95% CIs are presented instead of *P* values.

3. Results

3.1. Patients

Using the described criteria for baseline severity, 415 patients had mild depression, 385 moderate depression, and 265 severe depression. Patient disposition and reasons for discontinuations are summarized in Table 1. The Phase C completion rates were high in the mild, moderate, and severe groups (90.1%, 87.8%, and 86.0%, respectively). The most common reasons for discontinuation were withdrawal of consent and AEs. The mean daily dose of adjunctive aripiprazole at endpoint was 10.4 mg for patients with mild depression, 11.0 mg for those with moderate depression, and 12.1 mg for those with severe depression. Baseline demographics and psychiatric characteristics for randomized patients with mild, moderate, and severe depression are summarized in Table 2.

Baseline mean MADRS scores were in the ranges of 20.2–20.5 among mildly depressed patients, 27.2–27.4 among moderately depressed patients, and 33.7–34.6 among severely depressed patients. Baseline mean CGI-S scores were 3.8 among mildly depressed patients, 4.1 among moderately depressed patients,