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Aripiprazole as an adjunctive treatment for refractory unipolar depression

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Abstract

Introduction: Aripiprazole may be an effective adjunctive treatment in outpatients with unipolar depression that has been refractory to treatment with SSRI or SNRI medication.
Methods: Fifteen subjects with a current DSM-IV diagnosis of MDD which had not responded to SSRI or SNRI treatment were enrolled in a 12 week open-label study of aripiprazole with a maximum dose of 30 mg/day. Patients' current episode averaged 10.4 ± 16.6 years, with a range of 3 months to 54 years. Baseline severity averaged 30.1 ± 7.1 on HDRS-24, and 19.7 ± 8.4 on BDI. Patients had been treated with a mean dose of 79.2 ± 28.2 mg/day of fluoxetine equivalents for an average of 1 year prior to starting the study. Five subjects were on SNRI medications and 10 on SSRIs.
Results: Seven of 14 (50.0%) subjects were classified as treatment responders, as defined by at least 50% reduction in the HDRS-24 at week 12. Four subjects (28.6%) achieved remission, based on STAR*D criteria (HDRS-17 score ≤ 7). 26.7% (4/15) of subjects discontinued participation due to side effects. Two (40%) of 5 SNRI-treated subjects responded to aripiprazole augmentation.
Conclusions: These findings support previous studies for the effectiveness of aripiprazole in augmenting SSRIs or SNRIs in treatment-resistant major depression.

Keywords: Aripiprazole; Depression; Refractory; Treatment resistant

1. Introduction

As many as 29–46% of patients with major depression do not respond fully to treatment with single agents such as SSRI or SNRI antidepressants (Fava and Davidson, 1996; Fava, 2001). Residual symptoms of depression following treatment are associated with persistent psychosocial impairment, increased medical costs, increased psychiatric hospitalization and suicide. Numerous classes of agents, including lithium and thyroid hormone, have been studied as adjuncts for partial responders (Nelson, 2003; Ostroff and Nelson, 1999). Augmentation strategies using atypical antipsychotics, such as risperidone, ziprasidone, quetiapine, and olanzapine (Shelton et al., 2001; Klein et al., 2004) have been reported to be successful for treatment-resistant depression, and for obsessive compulsive disorder (Bystritsky et al., 2004). However atypical antipsychotic augmentation for treatment-resistant depression has been limited by side effects such as weight gain and parkinsonism (Shelton et al., 2001).

The pharmacological profile (McGavin and Goa, 2002; Potkin et al., 2003) of aripiprazole suggests it may be efficacious as an adjunct to SSRI or SNRI antidepressants. In particular, it has a unique receptor binding profile that combines partial agonist activity at D2 and 5HT1A receptors with potent antagonism at 5HT2A receptors (Shapiro et al., 2003). Aripiprazole's benign side effect profile (including minimal

Abbreviations: SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; MADRS, Montgomery-Åsberg Depression Rating Scale; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; BDI, Beck Depression Inventory; HDRS, Hamilton Depression Rating Scale; GAFS, Global Assessment of Functioning Scale; CGI, Clinical Global Impovement Scale; SAS, Social Adjustment Scale.

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weight gain, sedation and parkinsonism resulting from its low affinity for alpha-1-adrenergic, histamine (H1) and muscarinic (M1) receptors), suggests that it may be tolerable for refractory-depressed patients, who may need adjunctive treatment for a long period of time.

Several studies have suggested that aripiprazole is an effective adjunctive agent for treatment-resident depression. Recently Berman et al. (2007) reported a large multi-center double-blind 6-week study, demonstrating significant benefit of aripiprazole augmentation in comparison to placebo, with respective response rates (≥50% decrease on MADRS score) of 32.7% and 23.8%. Other studies include retrospective reviews (Barbee et al., 2004; Worthington et al., 2005) and open-label studies (Papakostas et al., 2005; Simon and Nemeroff, 2005) and a case report (Hellerstein, 2004). An open-label study at Massachusetts General Hospital reported that 5/9 (55.6%) patients with treatment-resistant depression responded after 8 weeks of aripiprazole augmentation (Papakostas et al., 2005). Simon and Nemeroff (2005) reported that depression remitted within 2 weeks for 9 of 15 patients whose standard antidepressant treatment was augmented with aripiprazole.

The STAR*D study, a 7-year effort of a highly representative clinical sample of depressed outpatients, has provided a plethora of information about treatment-resistant major depression. However, STAR*D did not assess the use of atypical antipsychotics for augmentation of treatment-resistant depression at any level of the study (Rush et al., 2006).

This study is a prospective open-label treatment of 15 patients with major depression unresponsive to a minimum of 6 weeks of a stable therapeutic dose of SSRI or SNRI medication. We hypothesized that adjunctive aripiprazole would be associated with improved depression response by clinician rating (as measured by the HDRS-24 item total score at week 12) and by patient self-report (as measured by the BDI at week 12). Additionally, we hypothesized that subjects would show an improvement on secondary measures of depression (BDI, SCL-90-R), and measures of psychosocial functioning (GAFS, CGI-Severity, CGI-Improvement, SAS) at week 12.

2. Methods

2.1. Subjects and study procedures

Participants were recruited through local advertisements and public service announcements for an outpatient study conducted at the St. Luke's Roosevelt Hospital Center Mood Disorders Research Unit. Inclusion criteria included: male and female outpatients between the ages of 18 and 70, principal DSM-IV diagnosis of major depressive disorder (MDD), unipolar, nonpsychotic type, score of 14 or higher on the 17-item Hamilton Depression Scale at baseline, and a minimum of 6 weeks of treatment with an SSRI or SNRI medication at an adequate dose. Patients met criteria for Stage I treatment-resistant depression (Fava and Davidson, 1996; Fava 2003), having failed to respond to at least one antidepressant trial of adequate dose and duration. Patients with the following DSM-IV diagnoses were excluded: delirium, dementia, amnesic or other cognitive disorders, bipolar disorder, cyclothymia, schizophrenia, delusional disorder, and anorexia nervosa or bulimia. Also excluded were patients with a diagnosis of substance abuse or dependence within the past 6 months, pregnant or nursing women, and patients who posed a serious risk for suicide during the study. Patients with unstable medical conditions (untreated, severe, or uncontrolled hyperthyroidism, hypothyroidism, hypertension, cardiovascular disease, diabetes, HIV, or seizure disorder) were also excluded.

Patients provided written informed consent prior to study participation. Following initial screening using the SCID DSM-IV interview (First et al, 1997) to evaluate diagnostic criteria, patients were clinically evaluated by a psychiatrist who obtained psychiatric and medical history, and laboratory testing including complete blood count, blood chemistry screen, urine drug screen, urinalysis, and thyroid function tests. Enrollees began a 12-week prospective, open-label trial of adjunctive aripiprazole while continuing their antidepressant medication or medications at the current dose. Patients were assessed by a psychiatrist at weeks 1, 2, 4, 6, 8, and 12, including symptoms, level of functioning, adverse experiences, concomitant medications, and vital signs. All evaluators assessing depression symptoms using the HDRS were trained to adequate inter-rater reliability prior to performing study evaluations.

2.2. Drug administration and concomitant medications

Subjects were started on 5 mg/day of aripiprazole. Patients unable to tolerate that dose were able to decrease dose to 2.5 mg/day, with subsequent increases as tolerated. Patients taking concomitant fluoxetine or paroxetine had the option of raising the dose of aripiprazole by 5 mg per week up to a maximum dose of 15 mg. All others were given the option to increase the dose of aripiprazole by 5 mg per week up to a maximum dose of 30 mg. Patients were not allowed to take any new psychotropic medication during the study, including bupropion, benzodiazepines, barbiturates, narcotics, or herbal preparations with putative psychotropic or sleep inducing effects. After visit 2, chloral hydrate or zolpidem was permitted for insomnia, not to exceed a total of 6 days. Previously initiated long-acting benzodiazepines were permitted to continue, if dosage was unchanged.

2.3. Clinical rating scales

At each visit, physicians administered the Hamilton Depression Rating Scale (HDRS-24 items) (Moberg et al., 2001; Hamilton, 1960), the Clinical Global Impressions Scale (CGI) (Guy, 1976), the Global Assessment of Functioning Scale (GAF) (American Psychiatric Association, 1994, pp. 32–33), and clinically-oriented safety and side effect evaluations. Patients completed self-report inventories including the Beck Depression Inventory (BDI) (Beck et al., 1961), the Symptom Checklist-90-Revised (SCL-90-R) (Derogatis et al., 1974), and the Patient-CGI (CGI-P) (Guy, 1976). In addition, at the initial and final visits subjects completed a self-reported measure of social functioning (Social Adjustment Scale, SAS) (Weissman and Bothwell, 1976; Weissman, 1999).