Neuropsychiatric Disease and Treatment

(South African Excerpts Edition)

volume 6 · number 2 · 2012

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Neuropsychiatric Disease and Treatment

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EDITORIAL

This quarter's journal focuses on psychopharmacology – three articles review various aspects of aripiprazole, a second generation antipsychotic with a unique mechanism of action, and topiramate, an anti-epileptic drug.

Berman et al report on original research conducted to determine the long-term safety and tolerability of aripiprazole as an augmentation medication in the treatment of major depressive disorder. Over 1000 participants were enrolled into an open-label 52-week study. Only 323 participants completed the study. The most common reasons for discontinuation were adverse events or lack of efficacy (n=365). The most common adverse events reported were weight gain and extra-pyramidal side effects. While this study reported that aripiprazole is safe and well tolerated overall in long-term use, it should be noted that the study was supported by a pharmaceutical company. More research is needed in this area.

Two expert opinions on aripiprazole are provided by McIntyre et al and Nelson et al. Nelson et al report on the use of aripiprazole as an augmentation strategy for treatment of major depressive disorder. This article suggests that this is a useful option, and that it has a better side-effect profile than other atypical antipsychotics. McIntyre et al report on the use of aripiprazole in the maintenance treatment of Bipolar Disorder, and conclude that there is as yet insufficient evidence of its efficacy, but that further study is worth pursuing.

Topiramate is being increasingly utilized in the prophylaxis of migraine. This expert opinion by Naegel and Oberman outlines the mechanism of action and suggests that it is a useful and well-tolerated treatment option at doses of 50-100mg daily. The authors did not find cognitive disturbance to be a common problem.

Adjunct Professor RGM Thom, Division of Psychiatry, Faculty of Health Sciences, University of the Witwatersrand

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CONTENTS

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EXPERT OPINION

ORIGINAL RESEARCH

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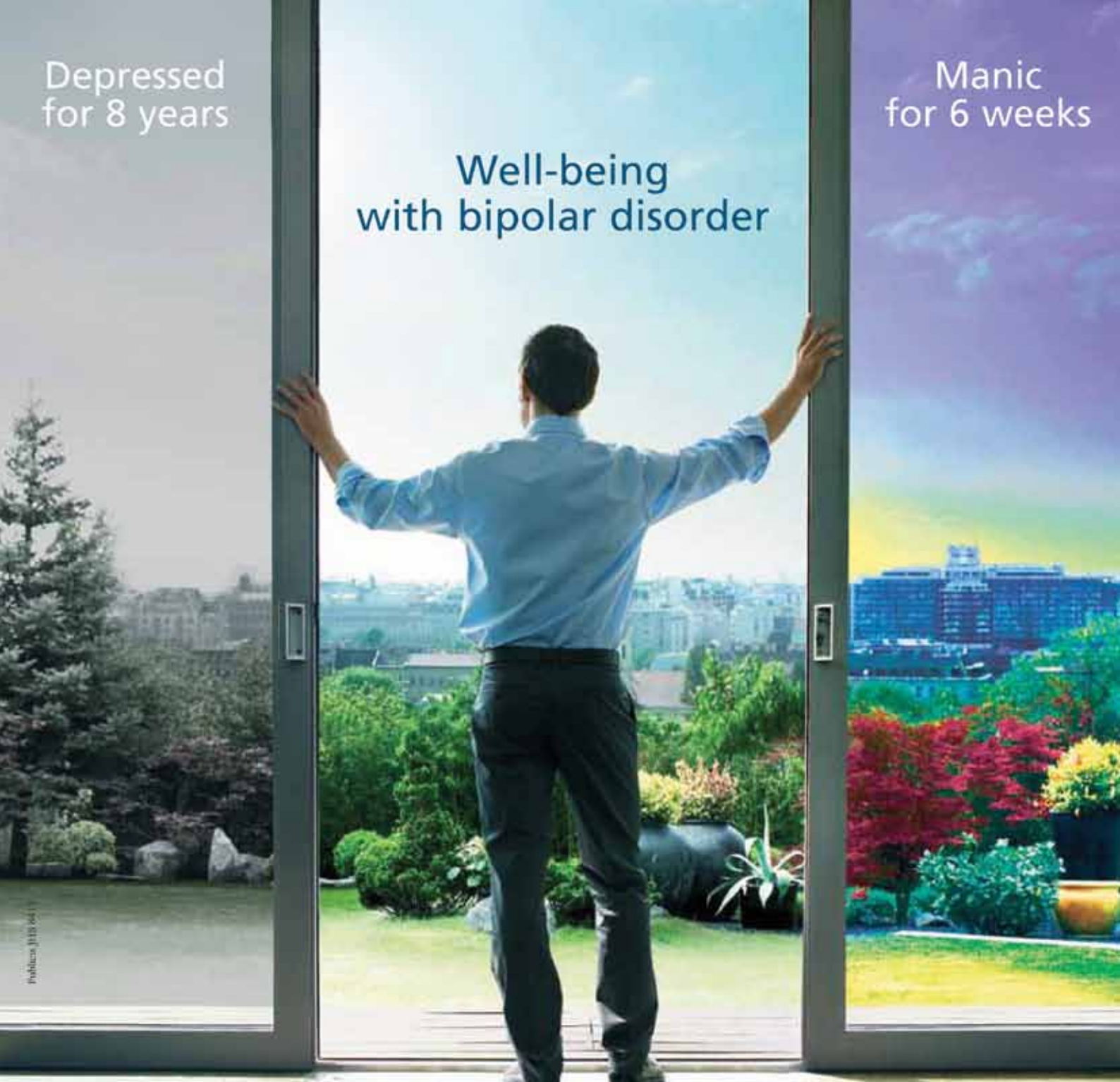

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EXPERT OPINION

Aripiprazole for the maintenance treatment of bipolar disorder: a review of available evidence

Roger S McIntyre[1,2,3,4]
Jinju Yoon[3]
Jeanette M Jerrell[5]
Samantha S Liauw[3]

[1]Department of Psychiatry, University of Toronto, Toronto, ON, Canada; [2]Department of Pharmacology, University of Toronto, Toronto, ON, Canada; [3]Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada; [4]Institute of Medical Science, University of Toronto, Toronto, ON, Canada; [5]Department of Neuropsychiatry and Behavioral Science, University of South Carolina School of Medicine, Columbia, SC, USA

Abstract: We aimed to review and synthesize results reporting on the maintenance efficacy of Aripiprazole in adults with bipolar I disorder. Aripiprazole is FDA approved for the acute and maintenance treatment of bipolar I disorder. Aripiprazole's efficacy during the long-term treatment of bipolar disorder is supported by extension of acute phase studies and long-term (ie, 100-week) double-blind placebo controlled recurrence prevention registration trials. Aripiprazole is not established as efficacious in the acute or maintenance treatment of bipolar depression. Moreover, aripiprazole's efficacy during the acute or maintenance phase of bipolar II disorder has not been sufficiently studied. Aripiprazole has a relatively lower hazard for metabolic disruption and change in body composition when compared to other atypical agents (eg, olanzapine, quetiapine). Moreover, aripiprazole has minimal propensity for sedation, somnolence and prolactin elevation. Aripiprazole is associated with extrapyramidal side effects, notably akathisia, which in most cases is not severe or treatment limiting. Future research vistas are to explore aripiprazole's efficacy in bipolar subgroups; recurrence prevention of bipolar depression; and in combination with other mood stabilizing agents.

Keywords: aripiprazole, bipolar disorder, maintenance, pharmacology

Introduction

During the past decade, the US FDA has approved several agents for the maintenance treatment of bipolar disorder (BD). Aripiprazole is approved as monotherapy and adjunctive treatment for the acute and maintenance treatment of adults with bipolar I disorder and for the treatment of pediatric mania. Several reviews have been published by ourselves and other groups pertinent to aripiprazole's efficacy in bipolar mania and depression and will not be reviewed herein.[1] Increasingly, the therapeutic emphasis in BD has been on the maintenance phase, largely due to increased recognition of the illness burden attributable to BD. Moreover, the long-term hazards of many psychotropic agents on body composition and metabolic parameters have differentiated aripiprazole as an alternative with a lower propensity toward adverse metabolic outcomes.

Methods

We conducted a PubMed search of all English-language articles published between January 1995 and January 2011. The key search term was aripiprazole combined with: randomized controlled trials, pharmacology, pharmacokinetics, pharmacodynamics, depression, mania, maintenance and BD. The search was augmented with a manual review of relevant article reference lists. We delimited our review to pivotal maintenance randomized controlled registration trials in BD.

Correspondence: Roger S McIntyre
Associate Professor of Psychiatry and Pharmacology, University of Toronto, Mood Disorders Psychopharmacology Unit, University Health Network, 399 Bathurst Street, Toronto, ON, Canada M5T 2S8
Tel +1 416 603 5279
Fax +1 416 603 5368
Email roger.mcintyre@uhn.on.ca

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Aripiprazole: pharmacokinetics/pharmacodynamics

Pharmacokinetics

Aripiprazole is available in oral compressed tablet, oral disintegrating tablet, non-refrigerated oral solution, and intramuscular formulations.[2] Aripiprazole tablets are available in 2-, 5-, 10-, 15-, 20- and 30-mg strengths. The effective dose range for patients with bipolar I disorder is between 15 and 30 mg/day. Orally disintegrating tablets are available in 10 mg and 15 mg strengths. In addition, aripiprazole is available in a 1 mg/mL non-refrigerated oral solution. Parenteral aripiprazole is intended for intramuscular use only and is available in several 7.5 mg/mL doses (ie, 5.25 mg/0.7 mL, 9.75 mg/1.3 mL, and 15 mg/2 mL) of clear, colorless, sterile, aqueous solution.[3] The oral formulation of aripiprazole is indicated for the acute and maintenance treatment of schizophrenia and BD, whereas the parenteral formulation is indicated for agitation associated with schizophrenia or bipolar mania.

The compressed tablets are extensively absorbed through the gastrointestinal tract with a bioavailability of 87%. The time to peak plasma concentration (T_{max}) is 3–5 hours for aripiprazole; food intake does not significantly affect peak plasma concentration (C_{max}) but may delay T_{max}.[4] Aripiprazole exhibits linear pharmacokinetics between the dosing ranges of 5–30 mg/day. At equivalent doses (ie, 30 mg/day), the plasma concentration of aripiprazole oral solution was higher than that of the compressed tablet, ie, the solution-to-tablet ratio of geometric C_{max} and area under concentration-time curve (AUC) values were 122% and 114%. Aripiprazole oral disintegrating tablets are bioequivalent to the compressed tablets. The time to peak plasma concentration with aripiprazole injection is 1–3 hours and has an absolute bioavailability of 100%. The geometric mean C_{max} achieved after an intramuscular (IM) dose was approximately 19% higher than the C_{max} of the oral tablet; the aripiprazole AUC in the first 2 hours after the initial IM injection is 90% greater than the AUC after a similar tablet dose. Over 24 hours of dosing, the systemic exposure is similar between aripiprazole injection and oral tablet administration.[3]

The half-life of aripiprazole is longer than other atypical agents, ie, 48–75 hours for aripiprazole and 94 hours for the active principal metabolite, dehydroaripiprazole. Steady state with aripiprazole is achieved within 14 days of administration.[4] The volume of distribution of aripiprazole is 404 L (4.9 L/kg) and it is extensively bound to plasma proteins (99%). Aripiprazole is metabolized mainly in the liver via the cytochrome P450 (CYP) enzymes 3A4 and 2D6, primarily via dehydrogenation, hydroxylation and N-dealkylation.[4] Approximately 40% of aripiprazole AUC in plasma is comprised of dehydroaripiprazole. Slow metabolizers at CYP3A4 or CYP2D6 exhibit an increase in C_{max} ie, an 80% increase in aripiprazole exposure and 30% decrease in active metabolite exposure and half-life (ie, 146 hours versus 48–75 hours) and will require adjustment of dosing.[4] Excretion of aripiprazole occurs via the kidney and liver with 25% and 55% of the dose recovered in the urine and feces respectively.[2,4]

Aripiprazole does not induce or inhibit CYP enzymes 3A4 and 2D6. Aripiprazole does not alter the pharmacokinetics of divalproex sodium or lithium and vice versa. Although renal and hepatic impairment results in an increase in C_{max}, dosage adjustment is not required. Although C_{max} and AUC is 30% and 40% higher respectively in women than men, no dosing adjustment is necessary.[2,4]

Pharmacodynamics

Aripiprazole is a highly lipid soluble quinolone-derived novel psychotropic agent.[5,6] Aripiprazole's receptor profile has been well characterized pre-clinically in vitro and in vivo.[7] Aripiprazole exhibits high receptor affinity for D_2 and D_3 receptors with moderate affinity for D_4 receptors. Aripiprazole acts as a partial agonist at the pre-synaptic dopamine autoreceptors and post-synaptic D_2 receptors (where it may have a higher intrinsic activity).[8,9] This in vitro profile provides for functional antagonism in hyperdopaminergic states and functional agonism in hypodopaminergic states.[10] Dehydroaripiprazole, has similar pharmacodynamic effects at the D_2 receptors.[7]

Aripiprazole exhibits high affinity for 5-HT_{1A} and 5-HT_{2A} receptors, resulting in partial agonism and antagonism respectively. The partial agonism at the 5-HT_{1A} receptor is similar to the anxiolytic azapirones.[11] Aripiprazole is an inverse agonist at 5-HT_{2B} receptors and a partial agonist at 5-HT_{2C}, 5-HT_7, D_3 and D_4 receptors. Aripiprazole displays low affinity for H1-histaminergic, muscarinic, cholinergic, and adrenergic receptors. This profile is predictive of low propensity to extrapyramidal symptoms (EPS), weight-gain, metabolic disruption, hyperprolactinemia and sedation.[12]

Aripiprazole: maintenance treatment in bipolar disorder

A single randomized, double-blind parallel group placebo-controlled study reported on the safety and efficacy of aripiprazole in preventing relapse of a mood episode in recently manic, or mixed episode patients with bipolar I disorder stabilized with aripiprazole.[13–15] This multiphase study

began with an open-label stabilization phase followed by a double-blind phase that extended to 100 weeks.

During the stabilization phase, patients received open-label treatment with aripiprazole 15 or 30 mg/day for 6–18 weeks. Patients meeting stabilization criteria [ie, Young Mania Rating Scale (YMRS) total score ≤10 and Montgomery Asberg Depression Rating Scale (MADRS) total score of ≤13 during 4 consecutive visits over a minimum of 6 weeks] were eligible for the double-blind phase in which they were randomized to the aripiprazole dose received at the end of the stabilization phase or placebo.

The primary efficacy parameter was time to relapse for a mood episode (ie, manic, depressive or mixed) during the double-blind phase. Relapse was defined by discontinuation due to inefficacy (ie, hospital admission due to mood episode), and/or addition to or increase in psychotropic medication other than study drug for manic and/or depressive symptoms. Secondary efficacy parameters were time to manic and depressive relapse and change from randomization to endpoint on continuous efficacy metrics [ie, YMRS, MADRS, Clinical Global Impression for use in bipolar illness (CGI-BP), and Positive and Negative Syndrome Scale (PANSS) total score as well as cognitive and hostility subscales].

Five hundred and sixty-seven patients entered the stabilization phase, which included 333 who had participated in earlier studies of aripiprazole. Of the total, 206 completed the stabilization phase, 161 entered the double-blind phase and 67 completed the double-blind phase. At 26 weeks, the mean aripiprazole dose was 24.3 mg/day. Most patients (71%) in both groups required at least one concomitant medication. Time to relapse was significantly longer for aripiprazole-treated patients than for placebo-treated patients ($P = 0.02$). The mean change from baseline to end-point in YMRS total score, PANSS cognitive subscale score and CGI-BP severity was superior in the aripiprazole-treated group compared to placebo.

More patients receiving placebo discontinued the study prematurely due to treatment emergent adverse events (TEAE) (19%) versus aripiprazole (10%). The five most commonly reported TEAEs (≥5%) in the aripiprazole-treated group were anxiety (17%), insomnia (16%), depression (12%), nervousness (10%), and tremor (9%). For placebo, the most commonly reported TEAEs were insomnia (19%), headache (17%), anxiety (15%), depression (15%), and manic reaction (13%). The rates of EPS were higher in the aripiprazole group; tremor was the most frequently reported EPS. A higher percentage of patients receiving aripiprazole had significant elevation of Simpson Angus Scale (SAS) and Barnes Akathisia Rating Scale (BARS) total scores.

Mean weight change from randomization to endpoint was −1.7+/−0.8 kg and +0.5+/−0.8 kg for placebo and aripiprazole, respectively. At the end of 26 weeks of treatment, significant weight-gain was observed in 13% of the aripiprazole treated patients and none of the placebo-treated patients. Aripiprazole-treated patients exhibited a non-significant decrease in mean serum prolactin concentration from randomization to end-point. No significant changes were noted in vital signs, corrected QT interval (QTc), fasting glucose, high-density lipoprotein (HDL), or low-density lipoprotein (LDL) concentration.

A 74-week extension study, which included the cohort from the 26-week study, was subsequently published. The inclusion and exclusion criteria of the extension study as weel as its definition of relapse were identical to the 26-week double-blind phase. In total, of the 67 patients who completed the initial 26-week double-blind phase, 66 entered the 74-week extension phase. During the 74-week extension, there were more discontinuations due to lack of efficacy from the placebo group (26%) than the aripiprazole group (13%). The mean aripiprazole dose during the combined 26-week and 74-week double-blind phases was 24.1 mg/day.

Time to relapse into any mood episode during double-blind treatment was significantly longer for patients who received aripiprazole than placebo. Time to manic relapse was significantly longer for aripiprazole treated than placebo treated patients. There were no differences in time to depressive relapses between groups. The mean change in YMRS total score from baseline of the double-blind phase to week 100 was significantly greater in the placebo versus the aripiprazole group. There were no differences between groups from baseline to week 100 in the total MADRS score. Improvements on the PANSS cognitive subscale score and PANSS hostility subscale were significantly greater for aripiprazole. The mean change from baseline to week 100 in the CGI-BP severity illness score was greater in aripiprazole treated subjects.

Adverse events related to EPS occurred more frequently with aripiprazole compared to placebo (22% versus 15%). The most common EPS were tremor (9% versus 1%), akathisia (8% versus 1%), and hypertonia (4% versus 2%). Mean change from baseline of the double-blind phase to week 100 on the SAS, AIMS, and BARS were not significantly different between groups. The mean weight change in patients treated with placebo was -1.9 ± 0.8 kg and 0.4 ± 0.8 kg with aripiprazole.

A separate randomized double-blind active agent and placebo-controlled study compared long-term efficacy and tolerability of aripiprazole with lithium monotherapy in the acute and maintenance treatment of bipolar I disorder.[17] Patients with acute bipolar mania or mixed states who required hospitalization were randomized to receive aripiprazole 15–30 mg/day, lithium 900–1500 mg or placebo for 3 weeks. At the completion of 3 weeks, those who had been randomized to placebo during the 3 week phase were blindly switched to aripiprazole whereas aripiprazole- and lithium-treated patients continued with their assigned treatment.

All patients continued double-blind treatment to week 12 at which time they could enter a 40-week double-blind extension phase. At week 12, 27%, 34%, and 29% of subjects receiving aripiprazole, lithium or placebo respectively completed the treatment. Improvement in mean YMRS total score was significantly greater with aripiprazole compared with placebo beginning at day 2 and extending to week 3. Lithium was associated with significant improvement compared to placebo at week 3. The most commonly encountered TEAEs with aripiprazole and lithium were headache (23% and 22% respectively), nausea (23% and 24%), akathisia (15% and 5%), sedation (13% and 7%), constipation (10% and 13%), and tremor (8% and 12%). There were no differences between aripiprazole and lithium treated subjects in total weight gain.

A separate 46-week open-label study evaluated the maintenance efficacy of aripiprazole in combination with lithium or valproate in the treatment of adults with BD.[18] This 46-week study represented an extension of a previous 6-week study evaluating the combination of aripiprazole with lithium or divalproex.[19] Patients with bipolar mania or mixed states with a partial non-response to lithium/valproate monotherapy (ie, YMRS total score $\geq$16 after at least 2 weeks of lithium/valproate monotherapy) were eligible for enrolment to receive either aripiprazole 15 or 30 mg or placebo for 6 weeks.

Efficacy was assessed by the mean change in the YMRS and MADRS total scores from the end of the 6-week double-blind phase to week 46. Of the 384 patients who were randomized to the 6-week double-blind treatment phase, 310 completed and 283 were eligible to enter the open-label extension phase. Of the 283 patients, 146 (51.6%) patients completed the 46-week open-label extension phase. The mean daily dose of aripiprazole during the extension phase was 17.9 mg/day.

Continued improvement in the YMRS total score throughout the open-label phase was noted from baseline to week 52. Overall reduction in MADRS score through the extension phase was minimal; as subjects were manic at study entry, the trial design is not sufficient to evaluate acute or prophylactic antidepressant effects.

Extrapyramidal side effects were reported in 24 (22.6%) of patients in the aripiprazole plus lithium group and 38 patients (21.8%) in the aripiprazole plus valproic acid group. The most commonly reported EPS were tremor and akathisia. Minimal changes were observed on the SAS, AIMS or BARS. Mean change in weight from the end of the 6-week double-blind phase to week 46 of the open label phase was 2.1 kg. Median changes in total cholesterol, LDL cholesterol and triglycerides during the study were not clinically significant.

The efficacy and safety of aripiprazole combined with lamotrigine was evaluated in the long-term maintenance treatment of individuals with bipolar I disorder, recently manic or mixed.[20] This two-phase study included a single-blind stabilization phase wherein subjects were stabilized with aripiprazole 10–30 mg/day + lamotrigine 100–200 mg/day. The stabilization period was up to 8 weeks. Individuals who were stabilized were randomly assigned to continue with aripiprazole + lamotrigine (n = 178) or lamotrigine + placebo (n = 173). More patients in the aripiprazole group (36.5%) than in the placebo (21.9%) group completed the study largely due to higher placebo discontinuation rate (31.2%) due to inefficacy. The mean dose of aripiprazole was 18.2 mg/day. The mean dose of lamotrigine was 172 mg/day. The primary efficacy end-point was time from randomization to relapse into a manic or mixed episode operationalized as hospitalization, symptomatic worsening of illness and/or discontinuation due to inefficacy. The aripiprazole combination treatment arm showed a lower relapse rate when compared to lamotrigine monotherapy, but the result did not reach statistical significance. A similar finding was demonstrated for time to relapse to any affective episode. In the mixed episode subpopulation, subjects receiving aripiprazole and lamotrigine had a significant delay in the time to depressive relapse compared with placebo + lamotrigine ($p = 0.041$). During the relapse assessment phase, there were no TEAEs in aripiprazole treated patients occurring in $>$5% of subjects and at twice the rate of placebo. The overall mean weight change at the end of the double-blind phase was 0.43 kg in the combination group versus −1.81 kg in the lamotrigine monotherapy group $p = 0.01$.

Recently, aripiprazole was compared to placebo as an adjunct to lithium or valproate for the maintenance treatment i.e. 52 weeks in bipolar I disorder.[21] Adjunctive aripiprazole treatment significantly delayed time to any relapse when compared with adjunctive placebo (hazard ratio = 0.54). Moreover the relapse rate for aripiprazole after 52 weeks was 17% and 29% with placebo. The most common TEAEs were headache, weight increase, tremor, and insomnia.

Summary

Aripiprazole is established as efficacious in the maintenance treatment of BD on the basis of monotherapy and adjunctive data. A consistent finding with aripiprazole is minimal change in body composition and metabolic parameters. Moreover, prolactin elevation is not encountered, nor is there any evidence of mood destabilization. Aripiprazole is associated with EPS (notably akathisia) which is usually mild and not treatment limiting. Aripiprazole has not been established as efficacious in the acute or maintenance treatment of bipolar depression.[22] Moreover, aripiprazole has two negative studies in acute bipolar depression.[20] BD is usually treated with polypharmacy; combination studies with extended maintenance phases with lithium and possibly antidepressants would be interesting for future research.

Disclosure

RS McIntyre is on the Advisory Board for Astra Zeneca, Bristol-Myers Squibb, France Foundation, GlaxoSmith-Kline, Janssen-Orth, Solvay/Wyeth, Eli Lilly, Organon, Lundbeck, Bioavail, Pfizer, Shire and Schering-Plough; is on the Speaker's Bureau for Janssen-Ortho, Astra-Zeneca, Eli Lilly, Lundbeck, Bioavail and Wyeth; has Continuing Medical Education activities with Astra-Zeneca, Bristol-Myers Squibb, France Foundation, I3CME, Solvay/Wyeth, Physicians' Postgraduate Press, CME Outfitters, Optum Health, Schering-Plough and Eli Lilly; receives research grants from Eli Lilly, Janssen-Ortho, Shire and Astra-Zeneca; and receives travel funds from Bristol-Myers Squibb.

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EXPERT OPINION

Augmentation treatment in major depressive disorder: focus on aripiprazole

J Craig Nelson[1]
Andrei Pikalov[2]
Robert M Berman[3]

[1]University of California San Francisco, San Francisco, California, USA; [2]Otsuka Pharmaceutical Inc., Rockville, MD, USA; [3]Bristol-Myers Squibb, Wallingford, CT, USA

Abstract: Major depressive disorder (MDD) is a disabling psychiatric condition for which effective treatment remains an outstanding need. Antidepressants are currently the mainstay of treatment for depression; however, almost two-thirds of patients will fail to achieve remission with initial treatment. As a result, a range of augmentation and combination strategies have been used in order to improve outcomes for patients. Despite the popularity of these approaches, limited data from double-blind, randomized, placebo-controlled studies are available to allow clinicians to determine which are the most effective augmentation options or which patients are most likely to respond to which options. Recently, evidence has shown that adjunctive therapy with atypical antipsychotics has the potential for beneficial antidepressant effects in the absence of psychotic symptoms. In particular, aripiprazole has shown efficacy as an augmentation option with standard antidepressant therapy in two, large, randomized, double-blind studies. Based on these efficacy and safety data, aripiprazole was recently approved by the FDA as adjunctive therapy for MDD. The availability of this new treatment option should allow more patients with MDD to achieve remission and, ultimately, long-term, successful outcomes.
Keywords: major depression, antipsychotic, mood disorder, aripiprazole

Introduction

Effective treatment of patients with major depressive disorder (MDD) remains an outstanding need in psychiatry. In the past, adjunctive antipsychotics were used primarily for treating psychotic symptoms in patients with MDD. However, current evidence indicates that these agents have antidepressant effects in patients with non-psychotic major depression. Recently, the atypical antipsychotic aripiprazole received approval from the Food and Drug Administration (FDA) as adjunctive therapy for patients with MDD. Given these developments, this review of the need for augmentation strategies, the range of options available, and the clinical evidence base for aripiprazole as the newest adjunctive medication for MDD was undertaken.

Epidemiology and disease burden

Major depressive disorder is a common and disabling psychiatric condition (Murray and Lopez 1996). Current estimates for lifetime prevalence of MDD range from 17% to 18%, making it one of the most prevalent mental health disorders (Kessler et al 2003). According to the Global Burden of Disease Study (Murray and Lopez 1996, 1997), depression currently ranks as the fourth leading cause of global disease burden, with the disorder affecting 13–14 million adults in the United States in a given year (Kessler et al 2003). By 2020, depression is projected to be the second leading cause of disease burden worldwide after heart disease. Furthermore, MDD is associated with high morbidity and mortality; for example, up to 15% of individuals with more severe forms of this disorder die by suicide (APA 2000). MDD also incurs huge health care costs: in 2000, depression (major depressive disorder, bipolar

Correspondence: J Craig Nelson
University of California San Francisco,
401 Parnussus Avenue, Box 0984-F,
San Francisco, CA 94143, USA
Tel +1 415 476 7000
Email craign@lppi.ucsf.edu

depression or dysthymia) incurred an estimated cost of US $83.1 billion, which was related to treatment costs, loss of productivity and suicide-related costs (Greenberg et al 2003). Another study that excluded bipolar depression found that employees with MDD have costs of lost work time totaling US$31 billion compared with peers without depression (Stewart et al 2003).

Depression comorbid with other chronic diseases, such as diabetes and arthritis, worsens overall health and well-being. Several studies have shown that there is an increased risk of major depression in individuals with one or more chronic diseases (Katon and Schulberg 1992; Noel et al 2004; Harpole et al 2005; Katon et al 2007). Indeed, data suggest that there is an interactive/synergistic effect between depression and chronic medical conditions, resulting in a negative effect on health beyond a simple additive effect of each condition (Moussavi et al 2007). In addition, depression aggravates the course of various medical conditions, even increasing mortality in patients with heart disease and stroke (Frasure-Smith et al 1993; Morris et al 1993).

If left untreated, depression may develop a chronic course or be recurrent, and over time be associated with increasing disability (Andrews 2001, Solomon et al 2000). Given the prevalence, chronicity and associated disability of MDD, there has been an increased focus on the development of new and more effective treatment options for this condition.

Diagnosis and neurobiology

MDD is a complex disease state with variable symptoms, presentation, features, and course. This variability is a challenge to the clinician and complicates diagnosis. The DSM-IV-TR defines MDD as the presence of single or multiple major depressive episodes once schizophrenia, schizoaffective disorder, delusional disorders, bipolar illness and episodes due to substance abuse or medical illness have been excluded (APA 2000).

Major depression is a heterogeneous disorder and, to date, causal mechanisms remain unclear. Psychological, biological, and environmental factors have all been shown to contribute to the development of MDD. For example, a recent review of twin studies estimated that about 37% of the risk of MDD is inherited (Sullivan et al 2000).

The early observation that many compounds that inhibit monoamine reuptake have antidepressant properties suggested that these neurotransmitters may be involved in the etiology of depression. Subsequently, many abnormalities in the serotonin, norepinephrine, and dopamine systems have been identified but it remains unclear which are primary, which are compensatory, and which are changes unrelated to depression (Belmaker and Agam 2008). A possible role for serotonin, norepinephrine, and dopamine in various behaviors associated with depression has been suggested by animal studies; yet, to date, these relationships have not been validated in depressed human patients. In fact, a comparison of the symptom effects of two antidepressants selective for different neurotransmitters – serotonin and norepinephrine – found no differences in the symptoms that improved, suggesting that they both may act through a final common pathway (Nelson et al 2005).

Alternatively, the role of neurotransmitters in the mediation of antidepressant action is relatively better established. Studies that use tryptophan depletion to lower serotonin and alpha-methyl-paratyrosine to inferfere with the synthesis of catecholamines indicate that serotonin, norepinephrine, and dopamine are involved in the mechanism of action of most antidepressant compounds (Delgado et al 1990; Miller et al 1996).

Treatment and management

Treatment goals

Once a patient is diagnosed with MDD, treatment of MDD should aim to achieve full resolution of symptoms and full restoration of psychosocial and occupational functioning. Treatment initially focuses on the rapid resolution of symptoms during the acute phase with the goal of remission. As the patient moves into continuation therapy, the goal is to maintain remission and prevent relapse. Remission represents a pivotal stepping stone on the road to recovery and is the key goal of pharmacological treatment (Figure 1).

Early achievement of symptomatic remission is critical to the long-term success of treatment (Kupfer 2005). Residual symptoms and partial response are associated with an increased risk of relapse, faster time to relapse, a more severe and chronic course, and increased functional impairment (social, occupational, home life) (Paykel et al 1995; Papakostas et al 2004). The importance of achieving remission has been well illustrated in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. As shown in Figure 2, at each treatment level, patients who achieved remission were less likely to relapse than those not achieving remission (Rush et al 2006; Rush 2007). Collectively, these data validate the importance of remission as a clinically meaningful endpoint.

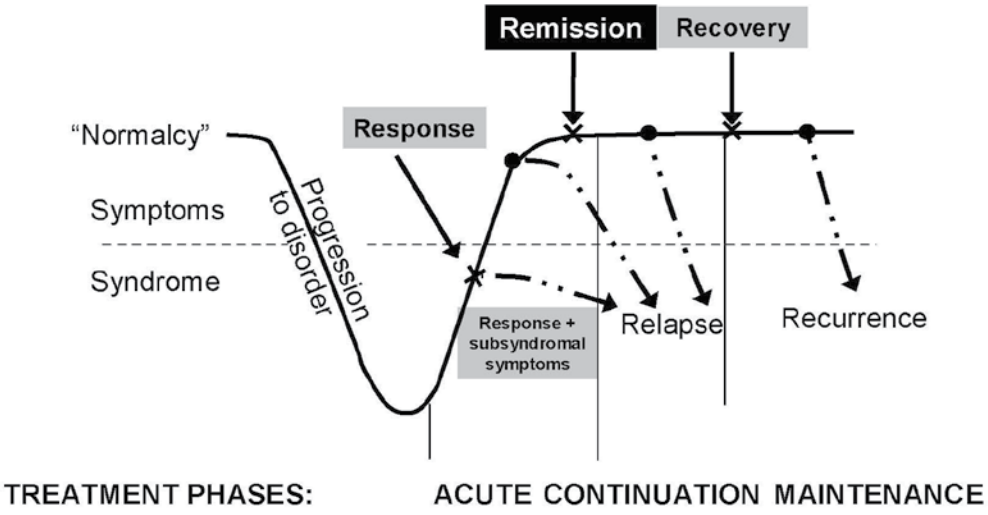

Figure 1 Remission is the key stepping stone between response to an acute episode and achieving full recovery (After Kupfer 1991).

Treatments

Antidepressants are currently the mainstay of treatment for depression and depressive episodes. Many different classes of antidepressants exist, including monoamine oxidase inhibitors (MOAIs), tricyclic antidepressants (TCAs), serotonin modulators, selective serotonin reuptake inhibitors (SSRIs), dopamine-norepinephrine reuptake inhibitors (DNRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and norepinephrine-serotonin modulators. The effectiveness of antidepressant medications is generally comparable. Although a possible advantage for dual-action agents has been suggested, a meta-analysis of 93 studies comparing dual-action agents with SSRIs found the advantage, although significant, was small, with a pooled response rate of 63.6% for dual-action agents vs 59.3% for SSRIs (Papakostas et al 2007b).

Despite the availability of more than two dozen different antidepressants, these treatments often yield inadequate results. Up to 70% of patients with MDD do not reach remission with an adequate course of one antidepressant and experience poorer long-term outcomes (Fava 2003; Rush et al 2006; Trivedi et al 2006). In addition, STAR*D demonstrated

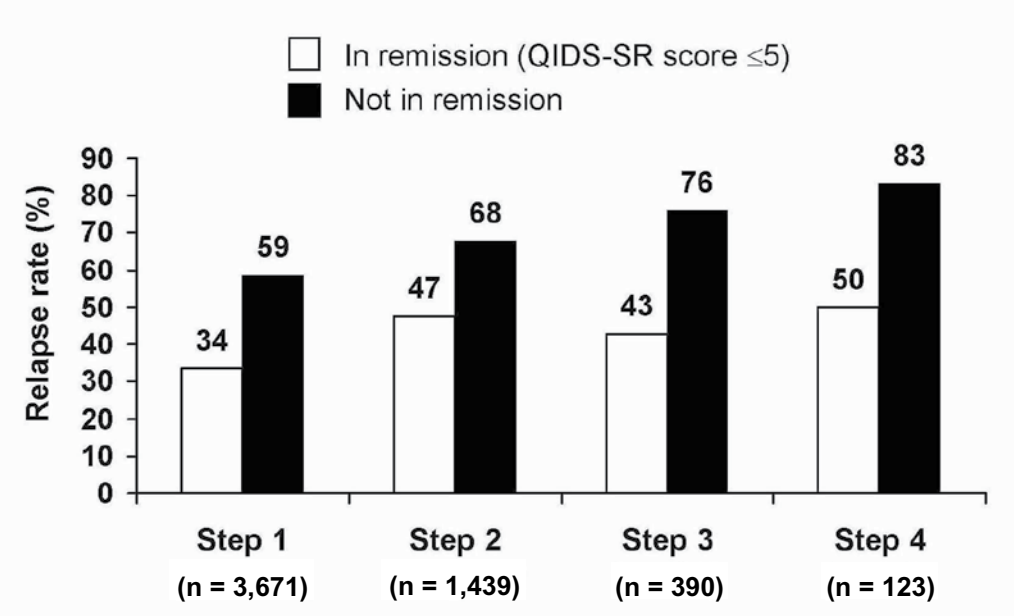

Figure 2 Remission at entry into follow-up was associated with lower relapse rates than response without remission in STAR*D study (12-month follow-up period) (After Rush et al 2006).
Relapse = QIDS-SR score ≥11.

that, with each failed treatment trial, remission rates declined. Remission rates after two or three failed treatments averaged less than 15% (Rush et al 2006).

According to American Psychiatric Association (APA) practice guidelines, if a patient with MDD has not responded to treatment or achieved only a partial response to treatment after 4–8 weeks of therapy during the acute phase, a change in dose, a switch to a new drug, or augmentation therapy is recommended (American Psychiatric Association 2000). A range of augmentation and combination strategies have been used (Fava et al 2003; Rush et al 2004). The challenge for clinicians is to tailor and adjust treatment options for individual patients in order to identify the most appropriate treatment approach.

Augmentation and combination strategies

Both augmentation and combination strategies have been used in patients with major depression. Combination strategies are those that use two antidepressants, each of which is approved as monotherapy. Augmentation strategies add an agent that is not conventionally used as first-line monotherapy (ie, atypical antipsychotic, lithium, T3) to an antidepressant. Augmentation and combination strategies have been proposed on the assumption that such combinations may have additive or synergistic effects (Rush et al 2006; Rutherford et al 2007). Furthermore, addition of a second agent in a partial responder has the practical advantage of maintaining any improvement made and may result in a rapid response. Notably, the efficacy of augmentation and combination treatments is not limited to partial responders, but has been less well studied in non-responders. For the purpose of this review article, we recognize the terms "augmentation" and "adjunctive" as similar in meaning and may use them interchangeably throughout the text.

Although combination approaches are commonly used, the evidence base is quite limited. The popular combination of bupropion and SSRI has not been examined in placebo-controlled studies. "Best evidence" is limited to an open-label, randomized comparison study in STAR*D (Trivedi et al 2006). Similarly, the best evidence for the combination of venlafaxine and mirtazapine is an open-label, randomized comparison (McGrath et al 2006). The combination of mirtazapine and an SSRI has been studied and found effective in two controlled studies of 26 and 62 patients, respectively (Carpenter et al 2002; Blier et al 2003). Desipramine added to fluoxetine has been demonstrated to be effective in a small study of 39 inpatients (Nelson et al 2004), but only half of the sample were previously treatment resistant. Overall, controlled trials of combination strategies are limited in number, are limited in sample size (largest is n = 62), and are variable in their requirements for prior treatment resistance.

A variety of agents have been used to augment antidepressants. The most frequently studied strategies are lithium, thyroid, stimulants, buspirone, pindolol, and omega-3 fatty acids. Addition of stimulants is one of the oldest strategies and most studies were small, open-label, and added dextroamphetamine or methylphenidate to a tricyclic or an MAOI. A recent placebo-controlled, double-blind trial in 60 patients augmented an SSRI with methylphenidate but failed to find a significant advantage for the augmentation approach (Patkar et al 2006a). Open-label studies of buspirone and pindolol suggested efficacy but a controlled trial of buspirone failed (Landen et al 1998), as did two controlled trials of pindolol in treatment-resistant patients (Moreno et al 1997; Perez et al 1999).

Lithium augmentation was the first approach suggested on the basis of a neurochemical rationale (De Montigny et al 1981). Subsequently, lithium augmentation has been studied in 10 placebo-controlled trials and a meta-analysis of these trials has been reported (Crossley and Bauer 2007). Although the meta-analysis showed evidence of efficacy, the value of lithium augmentation continues to be debated. The largest controlled lithium study included 61 patients but all the others were small studies ($\leq$35 patients). Few included clearly resistant patients, and the only study that did include treatment-resistant patients failed to find any advantage for lithium (Nierenberg et al 2003). Addition of triiodothyronine (T3) has also received considerable attention. A recent meta-analysis of T3 studies found evidence for efficacy; however, when limited to placebo-controlled trials, only 75 patients were studied in four trials and the difference between T3 and placebo was not significant (Aronson et al 1996). All of these controlled trials added T3 to a tricyclic antidepressant. In the open, randomized STAR*D comparison (Nierenberg et al 2006), thyroid was significantly better tolerated than lithium augmentation and appeared to be effective. The other augmentation strategy with a growing literature is the addition of omega-3 fatty acids. Although results were variable, a meta-analysis and review document only ten double-blind, placebo-controlled studies in 329 patients with mood disorders who were receiving omega-3 PUFAs for $\geq$4 weeks (Lin and Su 2007). The results demonstrated a significant effect for omega-3-fatty acid but significant heterogeneity was noted, as was an indication of publication bias. Study designs, patient samples, dosing, and omega-3 constituents

were variable. Finally, as with several other strategies, the efficacy of omega-3 in antidepressant-resistant patients needs further study.

Although other augmentation strategies have been suggested, the data for these are more limited. One large trial (n = 308) of modafinil in SSRI partial responders with prominent fatigue and sleepiness did show the drug to be more effective than placebo (Fava et al 2005). One controlled trial of folate in 127 depressed patients showed significant efficacy in women but not in men (Coppen and Bailey 2000). Augmentation studies of testosterone have been negative. Augmentation with estrogen or estrogen/progesterone combinations in post- or peri-menopausal women have been inconsistent (Morgan et al 2005, Dias et al 2006).

Atypical augmentation

Prior to 1980, more than 30 studies explored the use of typical antipsychotics in MDD (Nelson 1987). These trials are limited particularly by the use of earlier diagnostic systems; nevertheless, the findings suggested that patients experienced some relief with these agents. They were never recognized as true antidepressants, perhaps because they were not effective for treatment of two core symptoms of depression – loss of interest and motor retardation (Raskin et al 1970). Two formulations of an antipsychotic (perphenazine) and an antidepressant (amitriptyline) were licensed for use in depression. However, the use of the typical antipsychotics in non-psychotic depression declined rapidly during the 1980s with recognition of their risk of tardive dyskinesia.

The advent of second-generation antipsychotics with an improved safety profile has prompted their exploration as effective agents for the treatment of MDD. In 1999, Ostroff and Nelson reported the apparent value of adding risperidone in 8 outpatients who had not responded to an SSRI (Ostroff and Nelson 1999). In 2001, Shelton et al reported the first controlled study of olanzapine and fluoxetine vs either drug with placebo in 28 patients showing an advantage for the combination (Shelton et al 2001). Subsequently, a number of open and controlled studies followed. In 2007, Papakostas et al published a review and meta-analysis of atypical augmentation studies (Papakostas et al 2007a). They found 10 studies (olanzapine 5, quetiapine 3, risperidone 2). The studies included 4 smaller samples of 15–58 patients and 6 larger samples of 100–303 patients. All included patients with non-psychotic major depression. Different from the previous literature, several of these studies required evidence of prior treatment failure, usually to one historical and one prospective treatment trial. The meta-analysis found that the trials as a group demonstrated efficacy, although several individual studies did not (Figure 3). The risk ratio for remission comparing atypical antipsychotics with placebo was 1.75 (95% CI 1.36, 2.24; $p < 0.0001$) and for response was 1.35 (95% CI 1.13, 1.63; $p = 0.001$). Pooled remission rates were 47.2% and 22.3% for the atypical agents and placebo, respectively. Pooled response rates were 57.2% and 35.4%, respectively. Although this meta-analysis showed no difference in overall discontinuation rates between atypical antipsychotics and placebo, the rate of discontinuations due to adverse events was more than three-fold higher in patients treated with atypical antipsychotic agents than placebo ($p < 0.0001$).

Aripiprazole represents one of the most recently developed second-generation atypical antipsychotics. Efficacy for aripiprazole augmentation in depression was demonstrated in two large, randomized, double-blind 14-week studies (Berman et al 2007b; Marcus et al 2008). A third study is currently ongoing. Based on the findings to date, aripiprazole recently received approval from the FDA for the treatment of major depression as an adjunctive agent to standard antidepressant therapy (ADT). Initial open-label studies reported the efficacy of adjunctive aripiprazole in patients with depression (Barbee et al 2004; Papakostas et al 2005; Simon and Nemeroff 2005; Worthington et al 2005; Patkar et al 2006b; Hellerstein et al 2007; Pae et al 2007; Rutherford et al 2007; Schule et al 2007). An overview of the pivotal clinical trial program for aripiprazole in MDD is provided in Table 1. This program provides the most rigorous dataset available for any single agent evaluated for augmentation treatment of MDD, supported by large patient populations, randomized and placebo-controlled study designs, and implementation of historical and prospective demonstration of antidepressant unresponsiveness (Table 1). The remainder of this review focuses on the findings of these studies.

Focus on aripiprazole

Pharmacological rationale

Although the mechanism of action of augmentation is not well understood, it is possible that the distinct pharmacological profile of aripiprazole may make it a suitable adjunctive agent for the treatment of MDD. Differing from conventional antipsychotics, which were thought to have essentially a one-dimensional effect related to D_2 antagonism, the atypical drugs have neuropharmacologic profiles that are quite different and may have different implications in depression. Thus, although these agents appear to have

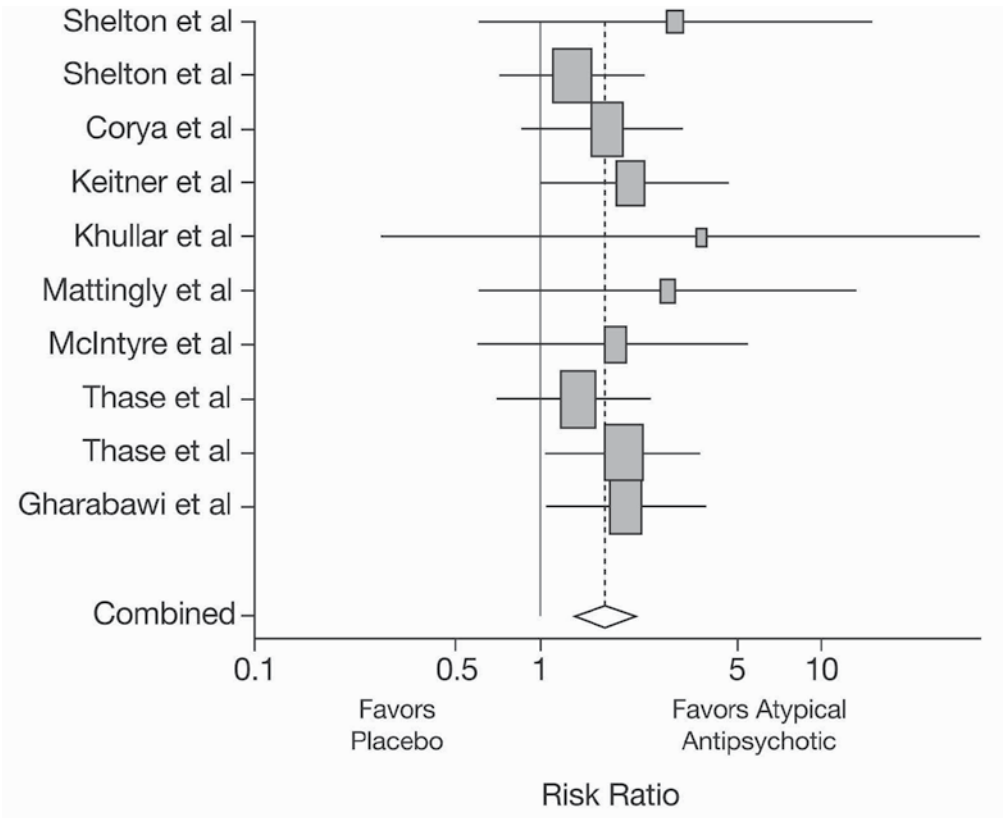

Figure 3 Meta-analysis of studies of atypical antipsychotic augmentation of antidepressants. Papakostas GI, Shelton RC, Smith J, et al 2007a. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry,* 68:826–31. Copyright © 2007 Physicians Postgraduate Press. Reprinted with permission.

similar efficacy in schizophrenia, it is not clear that they have similar efficacy in depression. For example, all of the atypical agents have 5-HT_2 antagonist effects that might contribute to antidepressant effects. The synergistic effects of olanzapine and fluoxetine on synaptic levels of 5HT, NE, and dopamine may be useful, and for ziprasidone the possible addition of 5-HT and norepinephrine reuptake blockade is of potential interest. For aripiprazole, the interesting features are its partial-agonist activity at the D_2/D_3 receptors, in addition to partial-agonist activity at the serotonin 1A (5-HT_{1A}) receptor (Shapiro et al 2003; Jordan et al 2004, Stark et al 2007). An agent, such as aripiprazole, that engages several mechanisms of action might be particularly effective in depression; however, all of these possible synergies are hypothetical and it is unclear how they translate into clinical efficacy.

Pharmacokinetics and dosing

Pharmacokinetic interaction studies have shown that aripiprazole 2–20 mg/kg does not affect the clearance of escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine; thus, no dosage adjustment is required for these antidepressants when aripiprazole is added. Across four studies, aripiprazole had no clinically meaningful effects on the pharmacokinetics of these standard antidepressant therapies (escitalopram, 10–20 mg/day; fluoxetine, 20–40 mg/day; paroxetine controlled-release, 37.5–50 mg/day; sertraline, 100–150 mg/day; or venlafaxine extended-release, 150–225 mg/day) in either healthy subjects or patients with MDD (personal communication/manuscript submitted). However, fluoxetine and paroxetine are both inhibitors of CYP2D6, and are likely to increase aripiprazole plasma levels (Abilify 2007). The pivotal augmentation studies used the same flexible-dose design. Patients randomized to receive adjunctive aripiprazole were treated with a starting dose of 5 mg/day, which could be increased weekly in 5 mg/day increments to a maximum dose of 15 mg/day (patients receiving fluoxetine or paroxetine CR, due to their CYP2D6 inhibition increasing aripiprazole levels) or 20 mg/day (all other patients) based on assessment of tolerability and clinical response. If tolerated, all patients were to receive a target minimum dose of 10 mg/day. Doses could be decreased at any visit, based on tolerability; patients unable to tolerate 5 mg/day could have their dose decreased to 2 mg/day. The FDA have approved an initial dose of adjunctive aripiprazole

Table 1 Overview of clinical data for aripiprazole in major depressive disorder

Study	Aripiprazole starting dose (permitted adjustment), mg	Comparator	Duration	Total n	Primary endpoint	Primary publication
CN138–139	5 (2–20)	Placebo	6 weeks	362	Mean change in MADRS from baseline to Week 6: –8.8 vs –5.8, $p < 0.001$	Berman et al 2007
CN138–163	5 (2–20)	Placebo	6 weeks	381	Mean change in MADRS from baseline to Week 6: –8.5 vs –5.7, $p = 0.001$	Marcus et al 2008
CN138–462	10 (10–20)	N/A	15 days	38	No meaningful effects on the pharmacokinetic parameters for venlafaxine (C_{max}, C_{min}, T_{max}, $AUC_{(TAU)}$) when administered alone and co-administered with aripiprazole	Boulton et al in press
CN138–463	10 (no adjustment)	N/A	15 days	25	No meaningful effects on the pharmacokinetic parameters for escitalopram (C_{max}, C_{min}, T_{max}, $AUC_{(TAU)}$) when administered alone and co-administered with aripiprazole	Boulton et al in press
CN138–164	Continuation dose from Studies CN138–139 and CN138–163	Placebo	52 weeks	930	Incidence of treatment-emergent adverse events	Berman et al 2008
CN138–165	5 (2–20)	Placebo	6 weeks	349	Incidence of treatment-emergent adverse events	Unpublished data

in patients with MDD of 2–5 mg/day, with a recommended target dose of 5–10 mg/day and a maximal dose of 15 mg/day. However, the relative efficacy of different doses has not been tested in MDD in fixed-dose studies. Some case studies have been published showing efficacy of aripiprazole augmentation at a dose as low as 3 mg/day (Terao 2007).

Efficacy

In patients with major depression without psychosis who showed an inadequate response to ADT, adjunctive aripiprazole has been shown to augment antidepressant efficacy in two 14-week, double-blind, randomized trials of identical design (Berman et al 2007b; Marcus et al 2008). The studies comprised a screening phase, an 8-week prospective treatment phase, and a 6-week randomization phase. During prospective treatment, patients received escitalopram, fluoxetine, paroxetine controlled-release, sertraline or venlafaxine extended-release, each with single-blind adjunctive placebo. Subjects with an inadequate response (<50% reduction HAM-D17 Total, HAM-D 17 ≥ 14 and Clinical Global Impressions-Improvement [CGI-I] ≥ 3 at the end of the ADT phase) continued ADT and were randomly assigned to adjunctive placebo or adjunctive aripiprazole; subjects were blinded to randomization (ie, the use of single-blind placebo). In the Marcus et al study, a total of 381 patients were randomized to adjunctive placebo (n = 190) or adjunctive aripiprazole (n = 191) in the randomized, double-blind treatment phase (Marcus et al 2008). In the Berman et al study, a total of 178 patients were randomly assigned to adjunctive placebo and 184 to adjunctive aripiprazole (Berman et al 2007b). It is also notable that, in both studies, the use of benzodiazepines or other sleep aids were not permitted, so that sedation/somnolence-inducing agents would not confound the efficacy results.

In both studies, remission rates (defined as a MADRS Total score of ≤10 and ≥50% reduction in MADRS Total score from baseline [end of prospective treatment]) were significantly higher with adjunctive aripiprazole than with adjunctive placebo: 26.0% versus 15.7%, $p = 0.01$ (Berman et al 2007b); and 25.4% versus 15.2%, $p < 0.05$ (Marcus et al 2008). Remission was achieved in significantly more patients with adjunctive aripiprazole versus placebo early in both studies, as early as week 1 (Berman et al 2007b) and week 2 (Marcus et al 2008).

Although remission is critical as an endpoint in real-life practice, for registration purposes the primary endpoint of these studies was the mean change in MADRS Total score from baseline to Week 6. Both studies showed significant improvements with adjunctive aripiprazole over placebo on this measure: −8.8 vs −5.8, $p < 0.001$ (Berman et al 2007b); −8.5 vs −5.7, $p = 0.001$ (Marcus et al 2008) (Figure 4). Again, the onset of a significant difference with adjunctive aripiprazole over placebo was apparent by week 1 in the study by Marcus et al (2008) and week 2 in the study

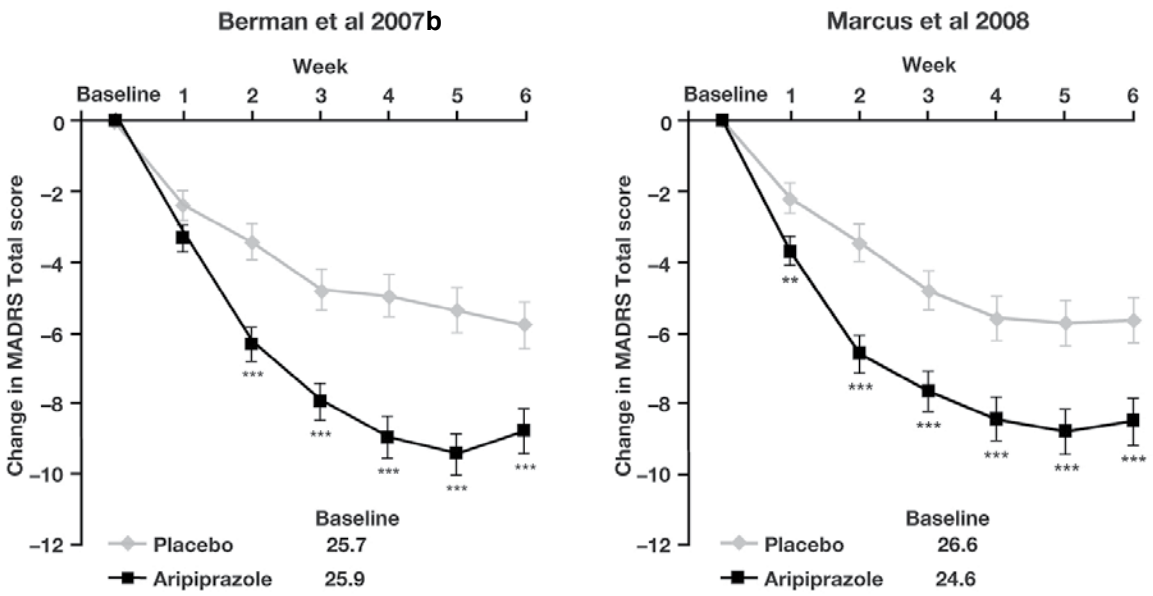

Figure 4 Change from baseline in MADRS Total score (last observation carried forward) in the two randomized, double-blind, placebo-controlled studies of adjunctive aripiprazole.
**p < 0.01 vs placebo.
***p < 0.001 vs placebo; MADRS Total score is rated from 0 to 60, where a negative change indicates improvement.
Abbreviations: MADRS, Montgomery – Asberg Depression Rating Scale; LOCF, last observation carried forward.

by Berman et al (2007b), with the adjunctive aripiprazole group continuing to show improvement throughout the study. Response, defined as ≥50% improvement in MADRS total score from baseline, was achieved by significantly more patients in the adjunctive aripiprazole than adjunctive placebo group in both studies at endpoint. Additional measures of efficacy – the Clinical Global Impression of Severity (CGI-S) scores and Clinical Global Impression of Improvement (CGI-I) response rates – showed significantly greater improvements with adjunctive aripiprazole compared with adjunctive placebo ($p < 0.05$).

Efficacy in difficult-to-treat subgroups

In a post-hoc analysis, data from the two double-blind efficacy trials (efficacy sample, n = 722) were pooled in order to determine the efficacy of aripiprazole in subpopulations of patients with MDD. Although it has been suggested that antidepressants may be less effective in anxious depression (Fava et al 2008) and that tricyclics may be less effective in atypical depression, adjunctive aripiprazole showed significantly greater efficacy than placebo in patients with anxious depression (defined by a total score of ≥7 on the anxious/somatization factor of the HAM-D17) or atypical depression (defined using the Inventory for Depressive Symptomatology-Self Rated (IDS-SR) to determine the presence of DSM criteria for Major Depression with Atypical Features) (Thase et al 2007). In addition, adjunctive aripiprazole was effective in both partial responders (≥25% but <50% improvement on the MADRS Total score) and minimal responders (<25% improvement on the MADRS Total score). Change scores on the MADRS Total score were −7.2 with aripiprazole and −5.4 with placebo in partial responders and −9.4 with aripiprazole and −6.0 with placebo in minimal responders (Thase et al 2007).

Tolerability

Overall in the clinical studies, adjunctive aripiprazole was well tolerated. There was a high completion rate in both studies (adjunctive aripiprazole, 87.9%; adjunctive placebo, 90.9% [Berman et al 2007b]; adjunctive aripiprazole, 84.8%; adjunctive placebo, 85.3% [Marcus et al 2008]), and a low discontinuation rate due to adverse events (AEs) (adjunctive aripiprazole, 3.3%; adjunctive placebo, 2.3% [Berman et al 2007b]; adjunctive aripiprazole, 3.7%; adjunctive placebo, 1.1% [Marcus et al 2008]).

Akathisia was the most common AE reported with adjunctive aripiprazole in the two samples occurring in 24.8% of the patients. However, a post-hoc pooled analysis of the 737 patients in the two studies showed that akathisia was of mild to moderate severity in 92% of the cases, only 3 of 371 aripiprazole-treated patients (0.8%) discontinued treatment because of it, and half of the akathisia events resolved at endpoint. The most common interventions associated with resolution were dose reduction (51%) and no intervention (36%) (Nelson et al 2007).

Because both of these studies used a "guided-flexible" dosing strategy that limited changes in aripiprazole dose to 5 mg in weekly increments and recommended a minimum dose of 10 mg/day, the rates of akathisia may overestimate rates obtained in clinical practice in which dosing is further individualized. Aiming for the minimum effective dose may be a prudent strategy. Indeed, in the Berman et al study, approximately half of the patients who completed the study and responded to adjunctive aripiprazole were receiving a dose of 10 mg/day or less (Berman et al 2007b).

Mean weight gain with adjunctive aripiprazole was higher than adjunctive placebo in both studies (+2.01 ± 0.17 kg vs +0.34 ± 0.18 kg, $p < 0.001$ [Berman et al 2007b]; +1.47 ± 0.16 kg vs +0.42 ± 0.17 kg, $p < 0.001$ [Marcus et al 2008]) over a 6-week treatment period. Importantly, no patients in either study discontinued treatment due to weight gain. Significantly, a pooled analysis of the metabolic parameters across both studies showed that the effects of adjunctive aripiprazole on mean change in body weight did not appear to be specific to any baseline body mass index category or to any dose of aripiprazole (Berman et al 2007a). Furthermore, the increase in body weight occurred in the absence of a clinically significant increase in other metabolic measures (Berman et al 2007a). During the double-blind, randomized treatment phase in Berman et al, two patients experienced suicidal ideation, both in subjects who were receiving placebo (Berman et al 2007a). In the second study, no suicide-related AEs were reported with either adjunctive aripiprazole or placebo during the double-blind randomized phase.

No new cases of tardive dyskinesia were observed during the study; however, the 6-week duration of the trials may underestimate rates observed with long-term treatment. Correll et al reviewed rates of tardive dyskinesia observed with the second-generation antipsychotics, and concluded that these rates (0.8% in non-elderly adults) were substantially lower than those observed with conventional agents (5.4% in adults on haloperidol) (Correll et al 2004). Nevertheless, tardive dyskinesia can occur with all antipsychotic agents. The rate of tardive dyskinesia in populations with MDD treated with aripiprazole in the 1-year safety study (0.4%) (Berman et al 2008) was comparable to what has been reported for other atypicals in other populations in long-term studies (0.8%; Correll 2004) and lower than that seen with olanzapine–fluoxetine combination (1.8%) (Corya et al 2003). All of the cases resolved within 45 days of discontinuing medication.

Functioning

In addition to efficacy for symptoms of major depression, an ideal treatment will also reduce or minimize functional disability associated with the disorder. The Sheehan Disability Scale (SDS) is an instrument used to assess the impact of illness-related impairment in three domains of functioning – work/school, social life, and family life/home responsibilities. Patients with MDD display greater functional impairment in social and family areas rather than work (Kessler et al 2003). Both the double-blind studies used the SDS and found that adjunctive treatment of standard ADT with aripiprazole improved family and social functioning (both $p < 0.05$). In addition, adjunctive aripiprazole treatment did not adversely affect sexual functioning in either study, as measured on the Sexual Function Index (SFI) scale, and resulted in significant improvements in 'interest in sex' ($p < 0.001$) and 'sexual satisfaction' ($p = 0.015$) items during one of the studies (Marcus et al 2008).

Conclusions

Achieving remission early in the course of depression is critical for the success of long-term treatment outcomes. A range of augmentation and combination strategies have been used in order to increase the chance of achieving remission. Indeed, for some patients, initiating combination and augmentation strategies earlier in treatment may increase the likelihood of remission; however, this strategy has not been well studied.

Although augmentation and combination strategies are commonly used for treatment of MDD, until recently there were relatively few large, double-blind, randomized, placebo-controlled trials to support this approach. As reviewed above, even the controlled trials used sample sizes that were usually very small. In addition, until recently treatment resistance was often poorly defined, if at all. The studies of the atypical antipsychotics are the first class of augmentation strategies to attempt to define unresponsive depression using adequate historical and prospective antidepressant trials. There is now growing evidence for the efficacy of atypical antipsychotics for adjunctive treatment of depressive symptoms of MDD in the absence of psychotic symptoms. In two large clinical trials, the addition of aripiprazole to standard ADT monotherapy was significantly more effective than the addition of placebo for the treatment of depression in patients with MDD who failed to respond to one prospective ADT trial and one to three historical trials during the current episode. Whether aripiprazole is more effective than other atypical agents has not been studied. Nor has the efficacy of aripiprazole been compared with lithium, thyroid or other augmentation

strategies. These questions, as well as the long-term use of these agents in depression, await further study.

Key clinical questions

How do you decide when to augment versus switch in MDD?

- Clinical wisdom, as reflected in surveys and treatment choice in STAR*D, suggests that augmentation is favored in partial responders. This is primarily based on practical considerations – namely, that addition of a second agent allows the initial response to be maintained while a switch might not.
- However, in patients with minimal response, data comparing augmentation strategies with switch options are lacking.
- The tolerability of the initial agent plays a role here. A poorly tolerated initial agent suggests a switch.

Is there an accepted definition of inadequate treatment response/partial response or treatment-resistant patients?

- No definition of treatment-resistant depression has been adequately validated.
- Lack of response to a minimum of two adequate trials of medication from different classes has been proposed as the basic definition of treatment resistance in MDD (Thase 2002).
- The STAR*D findings suggest that remission rates drop considerably after two failed trials, supporting the recommendation that two failed trials defines treatment resistance.

How does onset of action influence your decision when choosing a pharmacologic agent for MDD?

- Antidepressant medications are generally considered to have a delayed onset of action.
- In STAR*D, one half of the patients achieved remission during weeks 6–12.
- However, evidence of initial response can be observed in 1 or 2 weeks.
- Compared with switching, augmentation strategies may be more rapid, especially since no time is lost tapering the initial treatment.
- Early response to antidepressants is an unmet medical need and one that should be addressed in future treatment paradigms.

How can we manage side effects of adjunctive aripiprazole therapy?

- The key to successful treatment with any agent is awareness of the clinical profile and education of the patient about the drugs used.
- As clinical experience with aripiprazole has grown, some management strategies for the treatment of side effects have emerged.
- Although few predictors of akathisia have been identified, in patients with a history of akathisia, a more gradual dosing strategy might be used. Rates of akathisia appear higher in patients under age 40 years.
- For mild–moderate akathisia, dose reduction is an option if it does not compromise efficacy. If tolerable, akathisia appears to abate with time.
- Concomitant medications (eg, benzodiazepines, beta-blockers, or anticholinergic agents) may be useful for more severe akathisia but their efficacy in this situation is based more on clinical experience than controlled trials. Given high rates of improvement with time, it is not clear that these interventions are better than time.

Disclosures

During the past 12 months, Dr Nelson has been a consultant to or on the advisory boards of Bristol-Myers Squibb, Corcept, Eli Lilly, Merck, Orexigen; receives research support from NIMH; and receives no lecture honoraria. Dr Pikalov is an employee of Otsuka America Pharmaceutical, Inc. Dr Berman is an employee of Bristol-Myers Squibb.

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ORIGINAL RESEARCH

Long-term safety and tolerability of open-label aripiprazole augmentation of antidepressant therapy in major depressive disorder

Robert M Berman[1]
Michael E Thase[2]
Madhukar H Trivedi[3]
James A Hazel[4]
Sabrina Vogel Marler[5]
Robert D McQuade[6]
William Carson[7]
Ross A Baker[8]
Ronald N Marcus[9]

[1]Neuroscience Global Clinical Research Bristol-Myers Squibb, Wallingford, CT, USA; [2]Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, USA; [3]Division of Mood Disorders Research Program and Clinic, University of Texas Southwestern Medical School, Dallas, TX, USA; [4]Neuroscience Global Clinical Research, Bristol-Myers Squibb, Wallingford, CT, USA; [5]Global Biometric Sciences, Bristol-Myers Squibb, Wallingford, CT, USA; [6]Global Medical Affairs at Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA; [7]Global Clinical Development, Otsuka Pharmaceutical Development and Commercialization Inc, Princeton, NJ, USA; [8]Neuroscience Medical Strategy, Bristol-Myers Squibb Company, Plainsboro, NJ, USA; [9]Neuroscience Global Clinical Research, Bristol-Myers Squibb, Wallingford, CT, USA

Correspondence: Robert M Berman
Bristol-Myers Squibb,
5 Research Parkway, Wallingford,
CT 06492, USA
Tel +1 203 677 6914
Fax +1 203 677 7695
Email robert.berman@bms.com

Background: Effective management of major depressive disorder often includes the long-term use of multiple medications, and the longer-term utility and safety of adjunctive aripiprazole has not been evaluated in a controlled setting.

Patients and methods: Patients (n = 706) completing one of two 14-week double-blind studies of aripiprazole augmentation, as well as de novo patients (n = 296) nonresponsive to current antidepressant therapy, were enrolled in this open-label study. Patients received open-label aripiprazole for up to 52 weeks.

Results: Open-label treatment was completed by 323 patients (32.2%). At endpoint (n = 987), the mean dose of aripiprazole was 10.1 mg/day. Common (>15% of patients) spontaneously reported adverse events were akathisia (26.2%), fatigue (18.0%), and weight gain (17.1%). The incidence of serious adverse events was 4.0%. Four spontaneous reports of possible tardive dyskinesia were submitted (0.4%); all resolved within 45 days of drug discontinuation. Mean weight change was 4.4 kg; 36.6% experienced ≥7% increase in weight from baseline (observed case analysis, n = 303). No clinically relevant changes in other metabolic parameters were seen. At the end of open-label treatment, 221 patients (69.7%) had a Clinical Global Impression-Severity of Illness score of 1 (not at all ill) or 2 (borderline ill).

Conclusion: Long-term adjunctive aripiprazole therapy was well tolerated with an acceptable long-term safety and tolerability profile in patients with major depressive disorder who had not responded to treatment with one or more antidepressant therapies. Clinically significant weight gain was observed in about one-third of patients. Overall, the adverse event profile was consistent with that reported in the short-term trials and readily managed clinically.

Keywords: adjunctive aripiprazole, antidepressant therapy, major depressive disorder, long-term safety and tolerability

Introduction

More than 60% of patients with major depressive disorder do not achieve remission following treatment with an adequate course of at least one antidepressant.[1,2] For patients who do not obtain adequate benefit from antidepressant therapy, adjunctive therapy with an atypical antipsychotic is one treatment option.[3,4]

Aripiprazole, a partial agonist at the D_2/D_3 receptor and 5-HT_{1A} receptor, and a full antagonist at the 5-HT_{2A} receptor, is approved for use in the US as a treatment adjunctive to antidepressant therapy in adults with major depressive disorder. Results from three large, multicenter, randomized, double-blind, placebo-controlled trials demonstrated that aripiprazole treatment is effective and well tolerated as treatment adjunctive to antidepressant therapy in subjects with an inadequate response to a prospective

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eight-week trial of the same antidepressant therapy and at least one historical antidepressant therapy trial.[5–7] In these short-term major depressive disorder trials, adjunctive aripiprazole demonstrated a safety and tolerability profile similar to that seen in monotherapy studies of patients with schizophrenia[8] or bipolar mania.[9] Furthermore, the rates of discontinuation due to adverse events were low.[5–7] However, in order to prevent recurrence of major depressive episodes, patients with major depressive disorder may require long-term maintenance therapy. The utility, safety, and tolerability of long-term adjunctive aripiprazole therapy have not yet been studied.

The introduction of any new treatment strategy requires extra vigilance with regard to safety, particularly for combination treatment strategies where each class of medication has potential side effects.[10,11] Furthermore, augmentation of standard antidepressant therapies has the potential to induce, or even exacerbate, adverse events. Adverse events commonly seen with atypical antipsychotic monotherapy include weight gain, sedation, extrapyramidal symptoms, metabolic disturbances (eg, diabetes and hyperlipidemia) and hyperprolactinemia, although the risk varies between agents.[12–14] Understanding the longer-term safety and tolerability profile of adjunctive treatment is important in order to optimize clinical management and promote long-term adherence when appropriate.

This paper reports the findings from a 52-week, open-label trial that assessed the long-term safety and tolerability of aripiprazole adjunctive to antidepressant therapy. Assessment of tolerability was the primary objective of this study, and was evaluated by spontaneous reporting of adverse events, assessment of extrapyramidal symptoms using objective rating scales, and assessment of changes in body weight, fasting plasma lipids, and glucose levels. Specific efficacy findings from this long-term, open-label safety extension phase are also presented. Eligible patients included those who had been previously treated with adjunctive aripiprazole or placebo in two of the previous short-term trials,[5,6] as well as de novo subjects with a documented inadequate response to standard antidepressant therapy.

Methods

Study design and patients

This report includes data from a 52-week, open-label study to assess the long-term safety and tolerability of aripiprazole adjunctive to antidepressant therapy. In this reporting, duration of adjunctive aripiprazole dosing includes any exposure a patient may have received in the short-term trials, and any adverse events that may have emerged upon initiation of adjunctive aripiprazole treatment in those trials.

This study enrolled patients from two sources, ie, patients who had previously been enrolled in two 14-week, double-blind, placebo-controlled trials[5,6] (rollover patients), as well as de novo patients. Rollover patients entering this open-label study from the previously completed 14-week trials had to have had an inadequate response to a prospective antidepressant therapy treatment (venlafaxine, escitalopram, paroxetine, fluoxetine, or sertraline) at week 8 and have completed an additional six-week, randomized, double-blind period with adjunctive aripiprazole (aripiprazole rollover) or placebo (placebo rollover) treatment. Patients who had been antidepressant therapy responders at week 8, and thus were not eligible for randomization, could enter the open-label phase if they did not meet criteria for remission (Montgomery-Åsberg Depression Rating Scale [MADRS][15] $\leq$10) at week 14.

The patients were men and women, aged 18 years and older, who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision (DSM-IV-TR) criteria for a major depressive episode.[16] All rollover patients entering this open-label study met the following inclusion criteria at the time of entry into the previously completed double-blind study: they were required to have had a major depressive episode that had lasted at least eight weeks prior to inclusion with an inadequate response, defined as a $<$50% reduction in depressive symptoms severity, as assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire [ATRQ][17] to at least one but no more than three antidepressant therapy trials (each of at least six weeks' duration and at an adequate dose). Following screening, patients could then enter an eight-week prospective antidepressant treatment phase if they had a 17-item Hamilton Rating Scale for Depression (HAM-D-17)[18] total score $\geq$18 and could continue into the double-blind treatment phase if they had a HAM-D-17 total score that represented a $<$50% reduction in symptoms during prospective treatment, a HAMD-17 total score $\geq$14, and a Clinical Global Impressions-Improvement (CGI-I)[19] score $\geq$3. For entry into this long-term study, patients were also required to have the potential to benefit from further pharmacological adjustments (administration of adjunctive aripiprazole) based on the opinion of the investigator.

Inclusion criteria for de novo patients were similar to those for rollover patients, and included a duration of current depressive episode of at least eight weeks, an inadequate response indicated by a $<$50% improvement on the Massachusetts General Hospital Antidepressant Treatment

Response Questionnaire to at least one but no more than four antidepressant therapy trials (each of at least six weeks' duration and at an adequate dose) and a MADRS total score >10 at baseline and, in the opinion of the investigator, had residual symptoms that may have benefited from pharmacologic modification. De novo patients were also required to be currently taking antidepressant therapy at an adequate dose for a minimum of six weeks by the end of the screening phase. In addition to antidepressant therapies permitted in rollover patients, de novo patients were also permitted to be receiving mirtazapine, bupropion, bupropion sustained-release, bupropion extended-release, or duloxetine.

Both rollover and de novo patients were excluded if they had a current Axis I diagnosis of delirium, dementia, amnestic or other cognitive disorder, schizophrenia or other psychotic disorder, bipolar I or II disorder, eating disorder, or a clinically significant current Axis II diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder. Patients who posed a suicide risk were also excluded.

All subjects were required to provide written informed consent to participate and to be willing to discontinue all prohibited psychotropic medication (see below). The study was conducted in accordance with the Declaration of Helsinki, and the ethics committee at each site approved the protocol.

Study treatments

All rollover patients continued to receive their antidepressant therapy at the final prescribed dose in the previous trial in accordance with current product labeling, ie, escitalopram 10–20 mg/day, fluoxetine 20–40 mg/day, paroxetine controlled-release 37.5–50 mg/day (paroxetine 20–40 mg/day could be substituted if paroxetine controlled-release was not available), sertraline 100–150 mg/day, or venlafaxine extended-release 150–225 mg/day. De novo patients were permitted to receive these antidepressant therapies but could also receive bupropion sustained-release 300–400 mg/day, bupropion extended-release 150–450 mg/day, bupropion 300–450 mg/day, duloxetine 40–60 mg/day, or mirtazapine 15–45 mg/day. All patients were required to continue on their initial antidepressant therapy treatment and were not allowed to switch antidepressant medications during the course of open-label treatment. Dose adjustment of antidepressant therapy during the open-label treatment period was permitted for optimal therapeutic effect within the recommended dose range, although dose adjustment of antidepressant therapy should not be made within the same week as aripiprazole dose adjustment. Concomitant use of psychotropic agents (neuroleptics, anticonvulsants, antidepressants [other than continued antidepressant therapy], mood stabilizers, opioid analgesics, stimulants and barbiturates [except for migraine]) were prohibited during the study. Treatment of extrapyramidal symptoms (benztropine ≤6 mg/day, propranolol ≤120 mg/day) was also permitted during the study except within 12 hours prior to administration of movement rating scales. Clinically appropriate use of benzodiazepines and other hypnotics was permitted during the study (eg, diazepam, lorazepam, zolpidem, and zaleplon).

All patients, regardless of whether they received aripiprazole in the prior double-blind studies, started open-label, adjunctive treatment with aripiprazole 5 mg/day. If the 5 mg dose was well tolerated, the dose was increased to 10 mg/day at the end of week 1. The target dose of aripiprazole was 10 mg/day. Dose adjustments were made based on the clinical judgment of the investigator with respect to tolerability and therapeutic efficacy within the range 2–30 mg/day for patients receiving venlafaxine extended-release, escitalopram, mirtazapine or sertraline; or 2–15 mg/day for patients on fluoxetine, paroxetine, duloxetine, or bupropion (all CYP2D6 inhibitors).

Assessments and statistical analyses

Subjects had study visits at the end of weeks 1, 2, 4, 6, 8, 14, 20, 26, 32, 38, 44, and 52 during open-label treatment or at study termination. Safety was evaluated by monitoring of adverse events and vital signs (at each study visit), body weight (weeks 26 and 52,) and a 12-lead electrocardiogram (weeks 8, 26, and 52). In addition, extrapyramidal symptoms were evaluated using the Simpson-Angus Scale (SAS),[20] and Barnes Akathisia Clinical Assessment (BARS)[21] at weeks 4, 8, 14, 26, 38, and 52, and the Abnormal Involuntary Movement Scale (AIMS)[22] at weeks 4, 8, 14, 20, 26, 32, 38, 44, and 52.

Laboratory tests, including fasting metabolic parameters, were conducted at open-label treatment weeks 8, 26, 38, and 52. Metabolic changes were assessed by mean and median change from baseline to endpoint in fasting levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and plasma glucose.

Efficacy was assessed at every study visit using the Clinical Global Impression-Severity of Illness (CGI-S) rating scale (1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill).[19] No other efficacy assessments were conducted.

Safety analyses included all patients who received at least one dose of open-label study medication (safety sample), whereas efficacy analyses included all patients in the safety sample who had at least one CGI-S assessment in the open-label treatment phase (efficacy sample). All analyses were based on the last observation carried forward or observed case datasets.

For patients who had received aripiprazole during weeks 8–14 in the previously completed double-blind studies (aripiprazole rollover patients), baseline for assessment of adverse events, discontinuation due to adverse events, weight, metabolic measures, and extrapyramidal symptoms were defined at week 8 during the short-term trial (ie, prior to the first aripiprazole exposure). Thus, the maximum duration of aripiprazole treatment for rollover patients was 58 weeks (six weeks of double-blind aripiprazole treatment plus 52 weeks of open-label treatment). Demographic and disposition data for aripiprazole rollover patients used assessments from the week 14 visit from the previous study as the baseline measurement. For de novo and placebo rollover patients, baseline was defined using measurements from the start of aripiprazole treatment. Summary statistics for safety data are presented, including mean and standard deviation for continuous variables, and frequency and percent frequency for categorical variables. Rating scale scores are presented as mean change from baseline. No formal statistical testing was planned.

Results

Patient population and treatment

In total, 1076 patients (rollover, n = 706; de novo, n = 370) provided informed consent for study participation, of whom 1002 entered the open-label treatment phase (rollover, n = 706; de novo, n = 296). Patient disposition is shown in Figure 1 and the characteristics of patients included in the safety analyses are shown in Table 1. In total, 323 patients (32.2%) completed 52 weeks of open-label treatment; completion rates were similar between the rollover and de novo groups (Figure 1). Overall, the most common reasons for withdrawal from the open-label treatment phase were adverse events (23.0%), lack of efficacy/relapse (13.5%), and withdrawal of consent (12.5%). Time to discontinuation of aripiprazole due to any reason during open-label treatment is shown in Figure 2.

Treatment and dosing

The distribution of antidepressant therapy at study endpoint (n = 984) was consistent with the distribution at open-label study baseline and was as follows: escitalopram, n = 275 (27.7%); venlafaxine extended-release, n = 249 (25.1%); sertraline, n = 171 (17.2%); fluoxetine, n = 143 (14.4%); paroxetine controlled-release, n = 61 (6.1%); paroxetine, n = 29 (2. 9%); bupropion extended-release, n = 35 (3.5%); bupropion sustained-release, n = 11 (1.1%); duloxetine, n = 7 (0.7%); and mirtazapine, n = 3 (0.3%).

At endpoint (n = 987), the mean dose of aripiprazole was 10.1 mg/day for the total population. During the last four-weekly dosing interval during the open-label phase (open-label treatment weeks 48–52, n = 320), the distribution of adjunctive aripiprazole dosing was as follows: 2 mg/day, 10.9%; 5 mg/day, 25.6%; 10 mg/day, 28.8%; 15 mg/day, 20.3%; 20 mg/day, 7.2%; and >20 mg/day, 7.2%.

The most commonly used (>5% of patients) concomitant central nervous system medications during open-label treatment were other analgesics and antipyretics (57.0%), anticholinergics (10.6%), opioids (9.2%), hypnotics and sedatives (7.5%), and anxiolytics (7.2%). Overall, 15.2% of patients received concomitant medication for the potential treatment of extrapyramidal symptoms. These included propranolol (5.3%), amantadine (0.1%), benztropine (10.6%), and trihexyphenidyl (0.1%).

Adverse events

During long-term treatment, 931 (93.7%) patients experienced at least one adverse event. Treatment-emergent adverse events that occurred at an incidence ≥10% are shown in Table 2. The most common (>15% of the total population) adverse events with long-term adjunctive aripiprazole treatment were akathisia (26.2%), fatigue (18.0%), and weight increase (17.1%). The majority (75.2%) of treatment-emergent adverse events were mild or moderate in nature.

Overall, 226 (22.7%) patients in the safety sample discontinued study treatment due to adverse events; the rate of discontinuation was 23.7% for aripiprazole rollover patients and 22.4% for the placebo rollover/de novo patients. The most common adverse events leading to discontinuation (>1% of total population) were weight increase (3.3%), akathisia (3.3%), somnolence (2.0%), anxiety (1.7%), fatigue (1.7%), and sedation (1.1%); no other adverse events resulted in discontinuation of more than 1% of patients.

The incidence of serious adverse events was 4.0%; five serious adverse events occurred in two placebo rollover/de novo patients during long-term treatment (suicidal ideation, depression, chest pain, myocardial infarction, and intentional overdose); cellulitis, cholecystitis, and pneumonia were each also experienced by two patients (one placebo rollover/de novo patient and one aripiprazole rollover patient). There were no reports of neuroleptic malignant syndrome, completed suicide, or death due to other causes in this study.

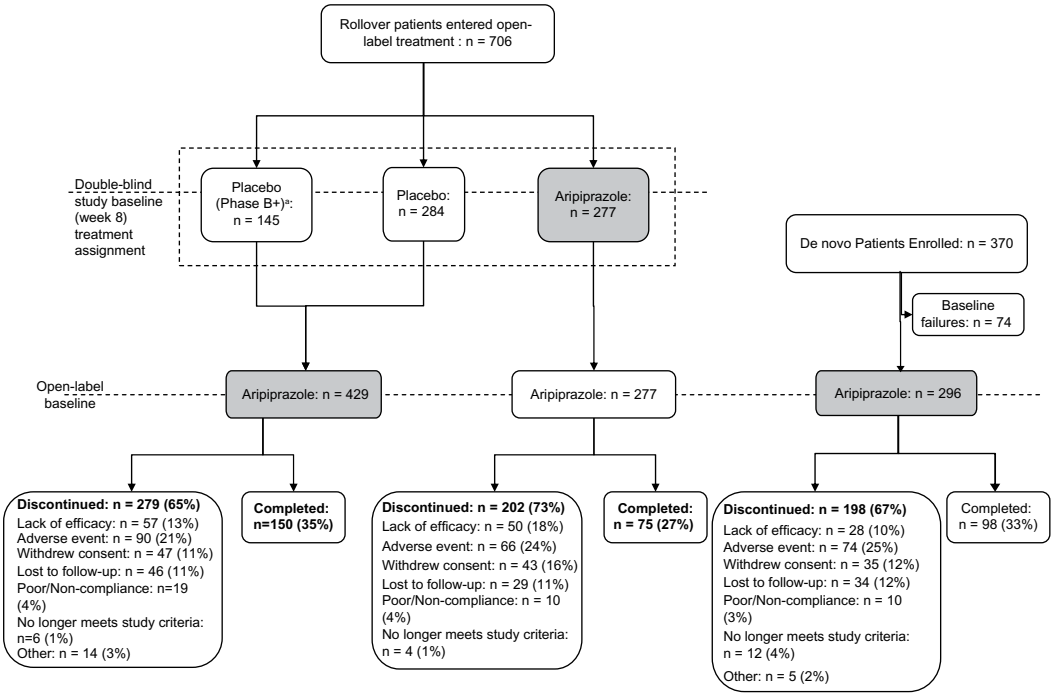

Figure 1 Enrollment, randomization, and disposition of patients.
Notes: Shaded boxes represent first aripiprazole dosing; [a]Patients in Phase B+ were antidepressant therapy responders at week 8 who received placebo for an additional six weeks.

Extrapyramidal symptoms

The rates of reported extrapyramidal symptom-related adverse events were as follows: dystonic events, 4.0%; parkinsonian events, 10.6%; akathisia events (ie, akathisia, psychomotor hyperactivity), 26.5%; dyskinetic events, 1.8%; and residual events, 2.2%. Akathisia occurred in 26.2% of this open-label population (placebo rollover/de novo patients, 24.0%; aripiprazole rollover patients, 31.8%) and the majority of cases had their onset within the first six weeks of treatment. Akathisia led to discontinuation in 3.3% of study patients. There were small mean changes from baseline in the AIMS, SAS, and BARS scores; mean change from baseline to week 52 (last observation carried forward) was 0.06 for the AIMS total score (mean baseline 0.07), 0.17 points for the SAS (mean baseline 10.32), and 0.11 for the BARS (mean baseline 0.15).

Four spontaneous reports of possible tardive dyskinesia were submitted during the study (0.4%); all the patients

Table 1 Open-label baseline[a] demographic characteristics (safety sample)

Demographic	n = 994
Age (years), mean (SD)	45.8 (11.3)
Gender, n (%) female	658 (66.2)
Race, n (%)	
White	906 (91.1)
Black	62 (6.2)
Asian	9 (0.9)
Other	17 (1.7)
Weight (kg), mean (SD)[b]	88.5 (22.6)
BMI (kg/m^2), mean (SD)[c]	31.2 (7.9)
Distribution, n (%)[c]	
BMI $\leq$ 24 (normal/underweight)	208 (21.0)
BMI 25–29 (overweight)	292 (29.4)
BMI $\geq$ 30 (obese)	492 (49.6)
Recurrent episode, n (%)[b]	776 (78.1)
MADRS total score, mean (SD)	20.2 (9.0)

Notes: [a]For rollover patients, assessments from the week 14 visit from the previous study served as the baseline measurement; for de novo patients, baseline was defined using the measurements from the start of the open-label study; [b]n = 993; [c]n = 992.
Abbreviations: SD, standard deviation; BMI, body mass index; MADRS, Montgomery-Åsberg Depression Scale.

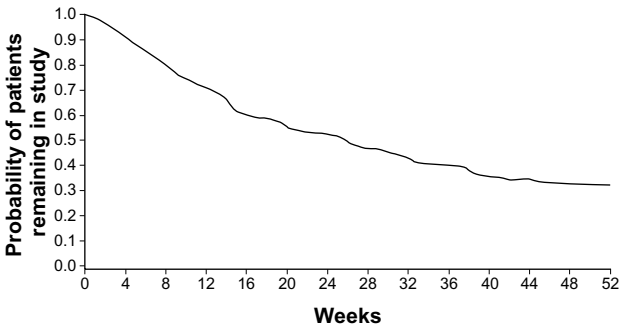

Figure 2 Time to discontinuation of aripiprazole due to any reason during open-label treatment, safety sample.*
Note: *Aripiprazole rollover patients had been exposed to aripiprazole for six weeks prior to open-label treatment.

Table 2 Treatment-emergent adverse events (≥10% of patients, safety sample)

Adverse event, n (%)	Placebo rollover/de novo patients (n = 720)	Aripiprazole rollover patients (n = 274)	Total (n = 994)
Akathisia	173 (24.0)	87 (31.8)	260 (26.2)
Fatigue	135 (18.8)	44 (16.1)	179 (18.0)
Weight increase	131 (18.2)	39 (14.2)	170 (17.1)
Restlessness	98 (13.6)	44 (16.1)	142 (14.3)
Insomnia	93 (12.9)	29 (10.6)	122 (12.3)
Somnolence	103 (14.3)	33 (12.0)	136 (13.7)
Headache	93 (12.9)	24 (8.8)	117 (11.8)
Upper respiratory tract infection	68 (9.4)	38 (13.9)	106 (10.7)
Nausea	77 (10.7)	18 (6.6)	95 (9.6)
Dizziness	73 (10.1)	18 (6.6)	91 (9.2)

Note: Reporting of adverse events for aripiprazole rollover patients includes any adverse events that may have occurred with aripiprazole treatment during the previous double-blind study period.

involved were receiving aripiprazole adjunctive to escitalopram. Interventions to manage tardive dyskinesia included dose reduction (n = 2) and drug discontinuation (n = 2). In all four cases, highest AIMS total scores were ≤4, and the symptoms completely resolved within 45 days of discontinuing adjunctive aripiprazole treatment.

Body weight

At week 26/32 (n = 491), the mean change in body weight from baseline (observed case) was 3.6 kg (placebo rollover/de novo patients, 3.4 kg; aripiprazole rollover patients, 4.3 kg). For the patients who completed 52/58 weeks of open-label adjunctive treatment (n = 303), the mean change in body weight over time showed that most weight gain occurred in the first 26–32 weeks on treatment. At week 26/32, the mean change in body weight was 4.0 kg, and at week 52/58 was 4.4 kg (placebo rollover/de novo patients, 3.9 kg at week 26, and 4.3 kg at week 52; aripiprazole rollover patients, 4.4 kg at week 32 and 4.9 kg at week 58). Mean change in body weight for aripiprazole rollover patients completing the study at week 6 was 1.8 kg. For aripiprazole rollover patients who had clinically significant weight gain (≥7%) at week 6, the mean change in body weight from baseline (observed case) was 8.7 kg at week 32 and 8.5 kg at week 58 (both n = 7). In aripiprazole rollover patients without clinically significant weight gain at week 6, mean change in body weight from baseline (observed case) was 4.0 kg (n = 106) and 4.5 kg (n = 64) at weeks 32 and 58, respectively.

Clinically significant weight gain (≥7%) occurred in 28.0% of patients (based on a last observation carried forward analysis) and 36.6% of subjects who completed the study (observed case analysis).

Metabolic effects

Figure 3 shows the mean change in fasting metabolic parameters from adjunctive aripiprazole baseline, by treatment period, for patients who continued to receive treatment (observed case analysis). National Cholesterol Education Program (NCEP)-defined cut-offs (see Figure 3) show that, on average, LDL, HDL, and glucose levels remained within normal limits. Baseline levels of cholesterol were higher, but tended to decrease over the 52-week exposure to aripiprazole. Baseline triglyceride levels were also above the normal 150 mg/dL criterion and remained above baseline throughout the course of aripiprazole treatment. Overall, there were no clinically important findings in the mean changes from baseline in fasting cholesterol, HDL, LDL, triglycerides, or glucose. For adjunctive aripiprazole exposure >46 weeks, the median change (range) in fasting metabolic parameters from adjunctive aripiprazole baseline were as follows: fasting cholesterol (n = 264), –4.0 (–154.0 to 90.0) mg/dL; fasting HDL (n = 264), –5.0 (–85.0 to 24.0) mg/dL; fasting LDL (n = 264), 1.0 (–117.0 to 94.0) mg/dL; fasting triglycerides (n = 264), 8.0 (–385.0 to 354.0) mg/dL, and fasting glucose (n = 262), 2.5 (–128.0 to 151.0) mg/dL.

The incidence of treatment-emergent potentially clinically relevant abnormalities in fasting total cholesterol levels (≥240 mg/dL) was 11.9% (n = 33/277) with adjunctive aripiprazole and 13.6% (n = 38/280) with adjunctive placebo during placebo-controlled trials and was 19.4% (n = 135/697) for a pooled population of patients treated with aripiprazole in both the short-term studies and this long-term trial. The incidence of treatment-emergent potentially clinically relevant abnormalities in fasting glucose levels (≥126 mg/dL) was 2.2% (n = 8/358) with adjunctive aripiprazole and 2.8% (n = 10/362) with adjunctive placebo during placebo-controlled trials, and was 4.9% (n = 44/906)

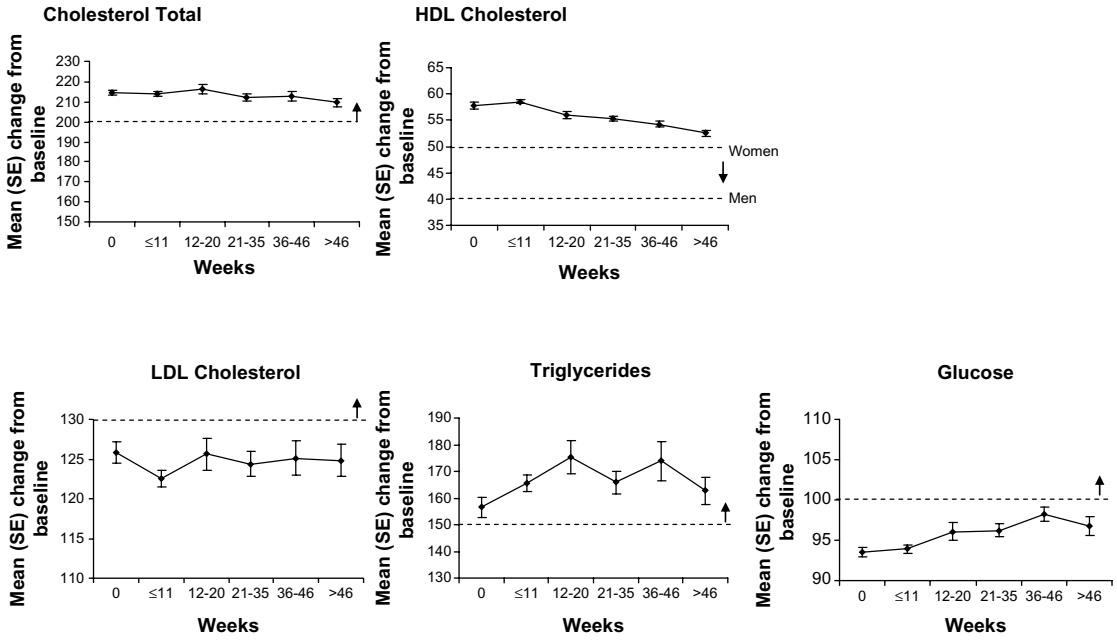

Figure 3 Time-course of fasting metabolic mean changes from baseline (observed case analysis).

Notes: Mean (SE) baseline values: fasting total cholesterol (n = 773), 214.6 (1.5) mg/dL; fasting HDL cholesterol (n = 773), 57.8 (0.6) mg/dL; fasting LDL cholesterol (n = 773), 125.8 (1.3) mg/dL; fasting triglycerides (n = 773), 156.5 (3.9) mg/dL; fasting glucose (n = 769), 93.5 (0.6) mg/dL. Dashed line and arrows represents abnormal lipid values (NCEP-defined criteria) and glucose levels (ADA criteria). Laboratory evaluations were performed at weeks 6, 14, 32, 44, and 58 for aripiprazole rollover patients, and weeks 8, 26, 38, and 52 for placebo rollover/de novo patients. For patients who had received aripiprazole in the previous double-blind study (aripiprazole rollover patients), baseline refers to week 8 scores from double-blind treatment.

Abbreviations: SE, standard error; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NCEP, National Cholesterol Education Program; ADA, American Diabetes Association.

for the pooled total population from short-term and long-term studies.

Vital signs and laboratory findings

The incidence of potentially clinically relevant vital sign and electrocardiographic abnormalities, as well as serum chemistry, hematology, and electrolyte measurements, was low. The exception to this was the incidence of potentially clinically relevant prolactin elevations at at least one blood draw (13.7%). For a number of these patients, there were relevant prolactin elevations at study baseline and aripiprazole treatment was associated with decreased prolactin levels. At week 52 (last observation carried forward), patients showed a mean decrease of 0.5 ng/dL in serum prolactin levels from baseline (12.9 ng/dL).

Efficacy

Mean CGI-S scores over the course of treatment showed sustained improvement in clinical symptoms, regardless of treatment during the double-blind study (Figure 4). At baseline, 33 patients (10.4%) had a CGI-S score of 1 or 2, indicating "normal" or "borderline ill" at adjunctive aripiprazole baseline, whereas at the end of open-label treatment (week 52/58) 221 patients (69.7%) had a CGI-S score of 1 or 2.

Discussion

Major depressive disorder is a chronic and recurrent condition that often requires patients to receive treatment for prolonged periods of time. As such, understanding the long-term tolerability profiles of treatments is essential for optimal clinical management. In this long-term study, the safety and tolerability of aripiprazole augmentation was demonstrated by relatively low discontinuation rates due to adverse events (23%) over a 52–58-week exposure. Furthermore, the adverse event profile was consistent with that reported in the short-term, double-blind, placebo-controlled trials.[23] Most adverse events were mild or moderate in severity and the incidence of serious adverse events was low. The incidence of vital sign/laboratory abnormalities was also low, with the exception of prolactin elevations. The effect of aripiprazole on prolactin elevation is difficult to interpret due to some patients having elevated levels at baseline, and a mean overall decrease in prolactin levels after treatment with adjunctive aripiprazole. Nonetheless, patients should be monitored for signs and symptoms of prolactin elevations due to the potential for sexual dysfunction and decreased bone mineral density.[24] Clinically significant weight gain during extended treatment was evident in a significant minority of patients, and weight gain was one of the most common adverse events with treatment.

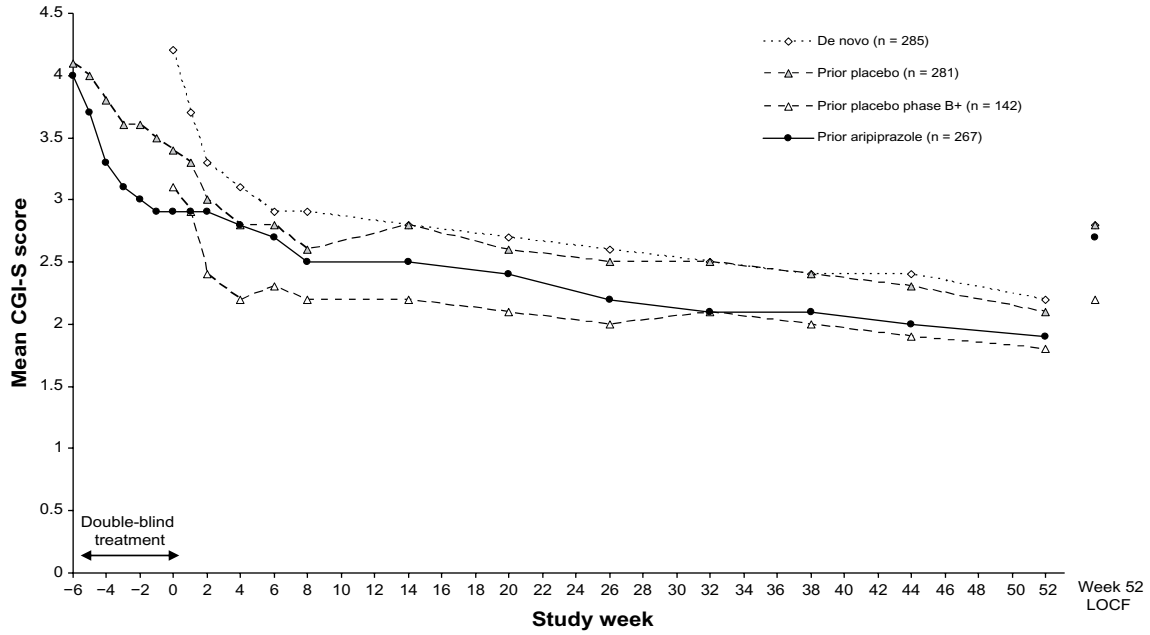

Figure 4 Mean CGI-S scores by treatment week.
Notes: Data by study week is from OC analysis; week 52 LOCF data are also shown. N numbers are week 52 (LOCF); weeks -6 to 0 represents CGI-S scores for aripiprazole rollover and placebo rollover patients during the previous double-blind study period; weeks 0 to 52 represent CGI-S scores during open-label treatment. Patients in the prior placebo Phase B+ group were ADT responders at week 8 who received placebo for an additional six weeks.
Abbreviations: CGI-S, Clinical Global Impression-Severity of Illness Scale; OC, observed case; LOCF, last observation carried forward; ADT, antidepressant therapy.

Although adjunctive aripiprazole was associated with a mean weight gain of 4.4 kg, the relative contribution of aripiprazole to weight gain compared with antidepressants alone is difficult to determine, because long-term administration of antidepressant medications is also associated with medically relevant weight gain.[25–28] For example, in one study, patients treated with fluoxetine for at least one year experienced a mean weight gain of 3.2 kg, and 25.4% had a clinically relevant weight gain (≥7%).[25] Interestingly, the rate of clinically relevant weight gain was similarly high for patients treated with placebo for the same duration.[25]

It is noteworthy that the aripiprazole rollover patients with clinically significant weight gain in the first six weeks of treatment experienced greater weight gain than patients without early weight gain. The majority of weight gain occurred over the first six months of treatment in both groups, suggesting that weight gain plateaus during long-term treatment. Regardless, patients receiving adjunctive aripiprazole over the longer term should be monitored for weight gain and should be proactively managed should it occur, especially given that the relative risk for long-term weight gain is not equal across all selective serotonin reuptake inhibitors.[10] Continued treatment in patients experiencing weight gain should be based on clinical assessment of the patient in the context of benefits and side effects.

Extrapyramidal symptoms and metabolic abnormalities are adverse events of great concern for patients taking antipsychotic medications over the long term. Adjunctive aripiprazole had minimal effects on blood lipid and glucose levels. There were no clinically meaningful increases in mean fasting metabolic parameters over the course of treatment and, on average, patients remained within, or slightly above, NCEP-defined "normal" limits. Similar shifts to "abnormal" levels of total cholesterol or glucose did occur within the first six weeks of treatment for patients treated with adjunctive aripiprazole and antidepressant monotherapy. Some additional shifts were observed over the course of the 52–58-week exposure, yet we cannot determine whether the shifts were directly related to aripiprazole, the antidepressant, or to the population already being overweight and obese at trial entry. Nonetheless, the data underscore the need for regular metabolic monitoring in patients with depression treated with adjunctive atypical antipsychotics. As for extrapyramidal symptoms, in this study, the rate of extrapyramidal symptom-related adverse events was not substantially different from that observed in the short-term, double-blind, placebo-controlled trials.[23] The objective movement disorder rating scales, AIMS, BARS, and SAS, did not reveal substantial evidence of extrapyramidal symptoms.

There were four spontaneous reports of tardive dyskinesia in this study; however, it is important to note that all four cases resolved with dose reduction or drug discontinuation. Given

that tardive dyskinesia is considered to be a chronic, persistent condition, the resolution of symptoms within 45 days of dose reduction or drug discontinuation may suggest that these cases of tardive dyskinesia were readily amenable to conventional intervention or the reports may have represented phenomena other than tardive dyskinesia. Given that tardive dyskinesia is a potentially serious adverse event, clinicians should remain mindful of the emergence of tardive dyskinesia with long-term adjunctive aripiprazole treatment, and take steps to manage patients who present with symptoms.

Of note, all patients started at 5 mg/day and were recommended to increase to 10 mg/day at the end of week 1. Although akathisia was the most common adverse event during long-term treatment, it rarely led to study discontinuation, and generally had its onset early in the course of treatment. Consideration of starting at a lower dose, such as 2 mg, with a slower titration schedule may reduce the incidence of extrapyramidal symptom-related adverse events, including akathisia.

Endpoint CGI-S scores suggest that adjunctive aripiprazole provides clinically meaningful, persistent efficacy with long-term treatment; nearly 70% of subjects who continued long-term treatment had a CGI-S score of 1 (normal) or 2 (borderline ill), indicating that scores are consistent with remission from symptoms. Regardless of previous treatment, all groups had a comparable mean endpoint score, suggesting a stability of effect over time. Also notable is the speed of onset of symptom relief. On average, most improvement in CGI-S scores occurred in the first month of treatment and was sustained over a year of treatment. However, conclusions on long-term efficacy of adjunctive aripiprazole treatment are limited, because this study was not designed to assess the maintenance of effect specifically; a double-blind study using a placebo-controlled discontinuation design will be necessary in order to establish longer-term efficacy.

The findings of this study are strengthened by the large overall patient population with major depressive disorder who received adjunctive aripiprazole treatment over 52–58 weeks of exposure. However, the findings reported here should be evaluated with consideration to several limitations, such as the open-label study design and the lack of a control treatment group, which limits the ability to attribute adverse events solely to adjunctive aripiprazole treatment because some adverse events may have resulted from the long-term use of the antidepressant therapies. It should also be considered that all patients were retitrated to aripiprazole 5 mg/day at entry into open-label treatment; this may have had an impact on the occurrence of adverse events for patients who were previously receiving a stable dose of aripiprazole during the parent studies. The impact of any effect of retitration on adverse events was not evaluated. Finally, patients benefiting from aripiprazole augmentation in this study were receiving a variety of different antidepressants, which were assigned based on investigator judgment. As such, the relative benefit of one antidepressant agent over the other has not been evaluated.

Conclusion

Overall, aripiprazole augmentation was well tolerated, with an acceptable long-term safety and tolerability profile in patients with major depressive disorder who had not responded to treatment with one or more antidepressant therapies. Common adverse events to consider during the long-term use of adjunctive aripiprazole for the treatment of major depressive disorder include weight gain and akathisia, although these events seldom led to treatment discontinuation in this study.

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Aspen and the Health Minister cycle "from the front" for children's healthcare

Aspen Group Chief Executive, Stephen Saad, and Minister of Health Dr Aaron Motsoaledi gave new meaning to the phrase "leading from the front" when they participated in the demanding inaugural 240 kilometer Aspen Trans Karoo mountain bike challenge from Ceres to Sutherland in the Western Cape. This race is recognized as one of the most grueling in the country, by virtue of the terrain and distance that needs to be traversed.

Saad and the Minister were raising funds for the newly established Sifiso Nxasana Paediatric Trust for the Children of Africa, created by Aspen following the untimely death of Sifiso Nxasana, son of Aspen's chairwoman, Dr. Judy Dlamini and her husband Sizwe Nxasana, CEO of FirstRand Ltd.

"The Minister demonstrated his commitment to raising funds for quality healthcare for the children of South Africa in the most practical and impressive way possible," comments Saad. "He led the field of cyclists and proved his enthusiasm and passion for public-private partnerships in addressing the shortage of paediatric healthcare in our country."

"South Africa has only one paediatric hospital in comparison with Canada's 23 and Australia's 19 and that is the Red Cross Children's Hospital in Cape Town," Saad points out. "The Trust will be raising funds for the Nelson Mandela Children's Hospital and the KwaZulu Natal Children's Hospital."

The Trans Karoo race was the first phase of the fund-raising campaign and reached the encouraging sum of R10 million. "We urge both local and foreign organisations and enterprises with interests in Africa to support the Trust," says Dr Motsoaledi. "If we truly believe the children are our future then we have a responsibility to ensure that all our youngsters, irrespective of culture or background, should have access to quality paediatric care in South Africa."

The race was won by former South African Iron Man, Raynark Tissink, with Hannele Steyn being the first woman across the finishing line.

Saad completed the course in just under 16 hours, expressing the great pleasure he experienced knowing that significant results had been achieved for children's healthcare.

Dr. Aaron Motsoaledi, Minister of Health; Stephen Saad, Aspen Group Chief Executive

From left to right: Sizwe Nxasana, CEO FirstRand Ltd; Dr. Aaron Motsoaledi, Minister of Health; Dr. Judy Dlamini, Aspen Group Chairwoman; Stephen Saad, Aspen Group Chief Executive; Stavros Nicolaou, Senior Executive, Aspen Pharmacare

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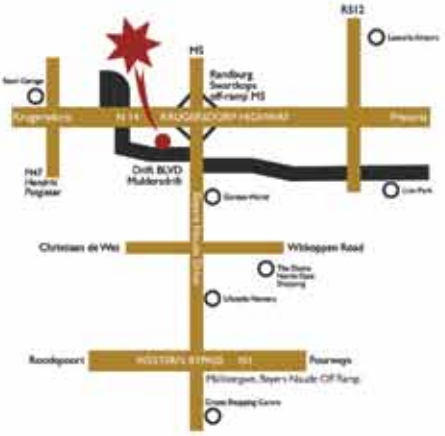

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