Aripiprazole for Depression

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Aripiprazole was approved by the FDA as an adjunct to antidepressants for the treatment of major depressive disorder in 2007. This article curates review papers, meta-analyses and randomized controlled trials on the role of aripiprazole as an augmentation strategy in the management of depression.

Review Articles

Aripiprazole: in major depressive disorder.

CNS drugs Weber J, Lyseng-Williamson KA, Scott LJ, Wolters Kluwer Health | Adis, Auckland, New Zealand. Published: 2008

Abstract: Aripiprazole, an oral quinolinone, is the first atypical antipsychotic agent to be approved in the US as adjunctive treatment in adult patients with major depressive disorder (MDD). In two large, well-designed trials in patients with MDD who had an inadequate response to standard antidepressant therapy, 6 weeks' adjunctive therapy with aripiprazole 2-20 mg/day improved mean Montgomery Asberg Depression Rating Scale (MADRS) total scores (primary endpoint) to a significantly greater extent than adjunctive placebo treatment. Improvements in mean MADRS total score during the double-blind phase favoured adjunctive aripiprazole treatment from 1-2 weeks onward, with per-protocol subgroup analyses showing that mean changes were not affected by the specific standard antidepressant therapy used, age or sex of the patient or the mean MADRS total scores at the start of double-blind adjunctive therapy. In general, secondary endpoint scores, including those for the Sheehan Disability Scale, Clinical Global Impression (CGI) Improvement scale and CGI Severity of Illness scale, improved to a significantly greater extent with adjunctive aripiprazole than with adjunctive placebo treatment, with significantly higher response and remission rates in the aripiprazole groups. In these two pivotal trials, adjunctive aripiprazole 2-20 mg/day was generally well tolerated, with most treatment-emergent adverse events being of mild to moderate severity.

Aripiprazole as adjunctive therapy for patients with major depressive disorder: overview and implications of clinical trial data.

CNS drugs Pae CU, Forbes A, Patkar AA, Department of Psychiatry, Bucheon St. Marys Hospital, The Catholic University of Korea College of Medicine, Bucheon, Kyounggi-Do, Republic of Korea. pae@catholic.ac.kr Published: Feb 2011

Abstract: Aripiprazole was initially approved to treat schizophrenia and later approved for bipolar mania, as a monotherapy and an adjunctive therapy (manic or mixed episodes), and for irritability associated with autism. Aripiprazole is a partial agonist at dopamine D(2) and D(3) and serotonin 5-HT1A receptors, and is an antagonist at 5-HT(2A) receptors. This profile, and convincing preliminary data from small-scale studies, provided the rationale for the large-scale exploration of aripiprazole for unipolar depression. Recently, three 6-week, large-scale, randomized, double-blind, placebo-controlled clinical trials demonstrated clinically meaningful efficacy for aripiprazole as an adjunctive therapy to antidepressants for treating major depressive disorder (MDD). In November 2007, aripiprazole was approved by the US FDA as an adjunctive therapy to antidepressants for treating MDD, with support from two of the above-mentioned trials. In the trials, aripiprazole was demonstrated to be safe and well tolerated, and showed a minimal trend for weight gain over the course of a 6-week treatment. The incidence of akathisia was higher than that reported in studies of patients with schizophrenia; however, most cases were mild to moderate and infrequently lead to discontinuation (5/1090 from all three trials). This comprehensive review provides an overview of the data from all three 6-week studies (including a pooled analysis) and from an unpublished 52-week, open-label extension study, to inform physicians and facilitate reasonable treatment decisions. In addition, specific issues associated with the use of aripiprazole as an adjunctive therapy in patients with MDD, including possible early treatment effect, appropriate timing of therapy initiation, appropriate dosing and duration of treatment, possible differential effect on depressive subgroups and long-term tolerability, are also discussed.

Neurobiological bases and clinical aspects of the use of aripiprazole in treatment-resistant major depressive disorder.

Journal of affective disorders Blier P, Blondeau C, University of Ottawa Institute of Mental Health Research, Canada. pierre.blier@rohcg.on.ca Published: Jan 2011

Abstract: Addition of atypical antipsychotics to the therapeutic regimen of patients with unipolar major depressive disorder not responding adequately to their treatment has become a common intervention. With all these agents the observation that low doses that are ineffective in schizophrenia, and thus not blocking dopamine D2 receptors effectively, indicate that their beneficial action is attributable to their action at other receptors. Preclinical research has shown that atypical antipsychotics can reverse the suppression of firing of norepinephrine neurons produced by selective serotonin reuptake inhibitors through their antagonism of 5-HT2(A) receptors. In the case of aripiprazole, three large placebo-controlled studies in more than 1,000 patients individually concluded to significant antidepressant responses and remissions after a six-week treatment. Aripiprazole addition did not produce more discontinuations due to adverse events than placebo. The most frequently encountered adverse events were akathisia and restlessness. Weight gain was minimal but significant in two of the three studies, suggesting that this side effect is not major problem. There was no significant laboratory abnormalities noted with this strategy. It is proposed that because of its long half-life (approximately 3 days), the doses of aripiprazole were escalated too rapidly in these controlled trials. More gradual titration may lead in routine clinical practice to better outcomes, minimizing side effects and improving remission rates.Copyright Â© 2011 Elsevier B.V. All rights reserved.

Current evidence for aripiprazole as augmentation therapy in major depressive disorder.

Expert review of neurotherapeutics Khan A, Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC, USA. akhan@nwcrc.net Published: Oct 2008

Abstract: Aripiprazole (Abilify) is the first atypical antipsychotic approved as adjunctive therapy for the treatment of major depressive disorder. The pharmacological basis of the action of aripiprazole in major depressive disorder remains unclear, but it may be related to its potent partial agonism of the dopamine D(2)/D(3) receptors, partial agonism of the 5-hydroxytryptamine (5-HT)(1A) receptor and antagonism of the 5-HT(2A) receptor. This article reviews findings on the efficacy and tolerability of aripiprazole from two identical placebo-controlled trials and from smaller open-label and retrospective studies. At doses of 2-15 mg/day aripiprazole was efficacious and well tolerated as adjunctive therapy to antidepressants in patients who had not responded to monotherapy.

Meta-analyses

Efficacy of adjunctive aripiprazole in patients with major depressive disorder who showed minimal response to initial antidepressant therapy.

International clinical psychopharmacology Nelson JC, Thase ME, Bellocchio EE, Rollin LM, Eudicone JM, McQuade RD, Marcus RN, Berman RM, Baker RA, Department of Psychiatry, University of California San Francisco, 401 Parnassus Ave, San Francisco, CA 94143, USA. CraigN@lppi.ucsf.edu Published: May 2012

Abstract: To evaluate the efficacy of adjunctive aripiprazole in patients with minimal response to prior antidepressant therapy (ADT). Pooled data from three randomized, double-blind, placebo-controlled studies assessing the efficacy of adjunctive aripiprazole to ADT in patients with major depressive disorder who had a minimal response [< 25% reduction on the Montgomery-Åsberg Depression Rating Scale (MADRS)] to an 8-week prospective ADT. During the 6-week, double-blind adjunctive phase, response was defined as at least 50% reduction in the MADRS score and remission as at least 50% reduction in MADRS score and a MADRS score = 10. Rates were examined using analysis of covariance and Cochran-Mantel-Haenszel tests. Kaplan-Meier curves were used to calculate time to response and remission. Of 1038 patients, 72% (n=746) exhibited a minimal response to ADT (ADT minimal responder). Time to response and remission were significantly shorter for ADT minimal responders receiving aripiprazole+ADT versus adjunctive placebo+ADT. ADT minimal responders on aripiprazole+ADT showed significantly greater improvements in MADRS score at endpoint compared with minimal responders on placebo+ADT (-10.3 vs. -6.5, P<0.0001). In addition, ADT minimal responders exhibited significantly higher response rates with aripiprazole+ADT than placebo+ADT (36 vs. 19%, respectively, P<0.0001) and higher remission rates (24 vs. 12%, respectively, P<0.0001). The numbers needed to treat with aripiprazole+ADT were six for response and eight for remission. Aripiprazole augmentation had a rapid and clinically meaningful effect in ADT minimal responders.

Aripiprazole in major depression and mania: meta-analyses of randomized placebo-controlled trials.

General hospital psychiatry Arbaizar B, Dierssen-Sotos T, Gómez-Acebo I, Llorca J, Unit of Mental Health, Hospital de Laredo, Laredo, Spain. Published:

Abstract: We performed meta-analyses to obtain pooled estimates from controlled clinical trials on the efficacy of aripiprazole in major depression disorder and manic phase of bipolar disorder.A search was performed in

Medline/PubMed using "aripiprazole" AND "depressive disorder" and "aripiprazole" AND "bipolar disorder" as keywords, and "randomized controlled trial" as limit. The last search was performed by April 30, 2009. References in the selected articles were revised to identify other studies. We selected four placebo-controlled clinical trials on aripiprazole's effect on major depression, and three on aripiprazole's effect on bipolar disorder. Studies performed in patients with comorbidity or devoted to measuring the effect of aripiprazole for maintenance therapy were excluded. We extracted, in duplicate, data on number of patients, withdrawals, changes in Montgomery-Asberg Depression Rating Scale and Young Mania Rating Scale (YMRS), response and remission rates, and side effects. Aripripazole is effective in increasing response rates in depressive patients (response rate in the aripiprazole group minus response rate in the placebo group: 7.7%, 95% CI: 1.5-14.2) and manic patients (difference in response rates: 15.7%, 95% CI: 9.7-21.8). It also improves by 3 points the scores in YMRS. Evidence of improving remission rates is unavailable. Some side effects were more frequent in patients taking aripiprazole; this was the case of akathisia, especially in depressive trials (rate difference: 20.3%, 95% CI: 16.9-23.7), and nausea in manic patients (rate difference: 10.5%, 95% CI: 7.4-13.5). Insomnia and restlessness were also more frequent in depressive patients taking aripiprazole We found evidence suggesting that aripiprazole is effective in both depressive and manic patients, but has relevant side effects. Further research is needed to identify its benefits for comorbid patients and its long-term effect.

Randomized Controlled Trials

Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants.

CNS spectrums Berman RM, Fava M, Thase ME, Trivedi MH, Swanink R, McQuade RD, Carson WH, Adson D, Taylor L, Hazel J, Marcus RN, Neuroscience Global Clinical Research at Bristol-Myers Squibb, Wallingford, CT 06492, USA. Robert.Berman@bms.com Published: Apr 2009

Abstract: Effective management of major depressive disorder (MDD) continues to be a challenging task for psychiatrists and primary care physicians. This trial evaluated the efficacy and safety of adjunctive aripiprazole versus antidepressant monotherapy in patients with MDD and independently replicated the positive findings of two similar trials. Patients (N=1,147) with MDD experiencing a major depressive episode and a history of inadequate response to antidepressant monotherapy were enrolled (week 0); 827 received single-blind adjunctive placebo plus open-label antidepressant (escitalopram, fluoxetine, paroxetine controlled release, sertraline, or venlafaxine extended release) for 8 weeks to confirm inadequate response to antidepressants; 349 patients with inadequate response were randomized (1:1) to double-blind, adjunctive placebo (n=172) or adjunctive aripiprazole (n=177; 2-20 mg/day). Primary outcome was the mean change in Montgomery-Asberg Depression Rating Scale (MADRS) Total score from baseline (week 8) to endpoint (week 14).Clinically significant improvements in depressive symptoms as assessed by decreases in the MADRS Total score were greater with adjunctive aripiprazole (-10.1) than placebo (-6.4; P<.001). Remission rates were greater for adjunctive aripiprazole than for adjunctive placebo (week 14, 36.8% vs 18.9%; P<.001). Completion rates with adjunctive aripiprazole and placebo were high (83% vs. 87%) and discontinuations due to adverse events were low (6.2% vs 1.7%).For some patients with MDD who do not obtain adequate symptom relief with antidepressant monotherapy, adjunctive therapies can significantly improve depressive symptoms. As reported, adjunctive aripiprazole was associated with a two-fold higher remission rate than adjunctive placebo. This, and previous studies, have shown that discontinuations due to adverse events were low and completion rates were high, and has indicated that both antidepressant and aripiprazole in combination were relatively well-tolerated and safe. This is the third consecutive clinical trial, in the absence of a failed trial, to demonstrate that aripiprazole augmentation to antidepressants is an efficacious and well-tolerated treatment for

patients with MDD who do not respond adequately to standard antidepressant monotherapy (ClinicalTrials.gov study NCT00105196).

The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study.

Journal of Clinical Psychopharmacology Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, Trivedi MH, Thase ME, Berman RM, Bristol-Myers Squibb, Wallingford, CT 06492, USA. Published: Apr 2008

Abstract: Nonresponse to one or more antidepressants is common and an important public health problem. This study evaluated the efficacy and safety of adjunctive aripiprazole or placebo to standard antidepressant therapy (ADT) in patients with major depressive disorder who showed an inadequate response to at least 1 and up to 3 historical and 1 additional prospective ADT. The study comprised a 7-28-day screening, an 8-week prospective treatment, and a 6-week randomization phase. During prospective treatment, patients experiencing a major depressive episode (17-item Hamilton Rating Scale for Depression total score > or = 18) received single-blind adjunctive placebo plus clinicians' choice of ADT (escitalopram, fluoxetine, paroxetine controlled-release, sertraline, or venlafaxine extended-release). Subjects with inadequate response were randomized to adjunctive placebo (n = 190) or adjunctive aripiprazole (n = 191) (starting dose 5 mg/d, dose adjustments 2-20 mg/d, mean end-point dose of 11.0 mg/d). The primary efficacy endpoint was the mean change in Montgomery-Asberg Depression Rating Scale total score from end of prospective treatment phase to end of randomized treatment phase (last observation carried forward). Mean change in Montgomery-Asberg Depression Rating Scale total score was significantly greater with adjunctive aripiprazole than placebo (-8.5 vs -5.7; P = 0.001). Remission rates were significantly greater with adjunctive aripiprazole than placebo (25.4% vs 15.2%; P = 0.016) as were response rates (32.4% vs 17.4%; P < 0.001). Adverse events occurring in 10% of patients or more with adjunctive placebo or aripiprazole were akathisia (4.2% vs 25.9%), headache (10.5% vs 9.0%), and fatigue (3.7% vs 10.1%). Incidence of adverse events leading to discontinuation was low (adjunctive placebo [1.1%] vs adjunctive aripiprazole [3.7%]). Aripiprazole is an effective and safe adjunctive therapy as demonstrated in this short-term study for patients who are nonresponsive to standard ADT.

The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study.

The Journal of clinical psychiatry Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, Khan A, Bristol-Myers Squibb Co., Wallingford, Conn. 06492, USA. Robert.Berman@bms.com Published: Jun 2007

Abstract: To assess the efficacy and safety of aripiprazole versus placebo as adjunctive treatment to standard antidepressant therapy (ADT) in patients with major depressive disorder (MDD) who showed an incomplete response to 1 prospective and 1 to 3 historical courses of ADT within the current episode.The study comprised a 7- to 28-day screening phase, an 8-week prospective treatment phase, and a 6-week double-blind treatment phase. Patients with DSM-IV-TR-defined MDD were enrolled between June 16, 2004, and April 27, 2006. During prospective treatment, patients received ADT: escitalopram, fluoxetine, paroxetine controlled-release, sertraline, or venlafaxine extended-release, each with single-blind, adjunctive placebo. Incomplete responders continued ADT and were randomly assigned to double-blind, adjunctive placebo or adjunctive aripiprazole (2-15 mg/day with fluoxetine or paroxetine; 2-20 mg/day with all others). The primary efficacy endpoint was the mean change from end of

prospective treatment to end of double-blind treatment (week 14, last observation carried forward) in Montgomery-Asberg Depression Rating Scale (MADRS) total score (analysis of covariance).A total of 178 patients were randomly assigned to adjunctive placebo and 184 to adjunctive aripiprazole. Baseline demographics were similar between groups (mean MADRS total score of 26.0). Mean change in MADRS total score was significantly greater with adjunctive aripiprazole (-8.8) than adjunctive placebo (-5.8; $p < .001$). Adverse events (AEs) that occurred in > or = 10% of patients with adjunctive placebo or adjunctive aripiprazole were akathisia (4.5% vs. 23.1%), headache (10.8% vs. 6.0%), and restlessness (3.4% vs. 14.3%). Discontinuations due to AEs were low with adjunctive placebo (1.7%) and adjunctive aripiprazole (2.2%); only 1 adjunctive aripiprazole-treated patient discontinued due to akathisia.In patients with MDD who showed an incomplete response to ADT, adjunctive aripiprazole was efficacious and well tolerated. ClinicalTrials.gov identifier NCT00095823.

Related information

- Aripiprazole Indications: FDA-Approved and Off-Label Uses
- Aripiprazole Lauroxil Extended-Release Injectable (ARISTADA)
- Mechanism of Action of Aripiprazole
- Pharmacokinetics of Aripiprazole: Clinical Summary
- Aripiprazole for Schizophrenia
- Aripiprazole for Mania