Review Articles :

"Aripiprazole, a new generation antipsychotic: current research and clinical practice

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ABSTRACT

Aripiprazole is the new generation class of antipsychotic. Chemically, aripiprazole is a quinolinone derivative. Aripiprazole gives its action through the partial agonist mechanism at dopamine D_2 and 5- HT_{1A} receptors, and is also an antagonist at 5-HT_{2A} receptors. Preclinical and placebo controlled trials of aripiprazole have evaluated that aripiprazole is effective in the treatment of schizophrenia. Comparative trials of aripiprazole with typical and atypical antipsychotics have shown that aripiprazole has similar efficacy as haloperidol and olanzapine. Data also suggest that aripiprazole is safe and its tolerability profile is good. This molecule is also showing promising results in the treatment of bipolar disorders but the evidence is still inadequate. This article critically examines the various clinical trials conducted in various countries regarding the therapeutic profile of aripiprazole.

INTRODUCTION

Aripiprazole is the first next generation atypical antipsychotic with a mechanism of action that differs from conventional and atypical antipsychotics. Aripiprazole belongs to a new class of antipsychotics, called dopamine system stabilizers. Dopamine system stabilizer reduce the hyperactivity of dopamine neurons that mediate psychosis and at same time restore dopamine activity in the cortical regions that mediate negative and cognitive symptoms as well as the brain area that regulate motor movements and prolactin. [1] Collectively, aripiprazole is an important new atypical antipsychotic candidate with a favourable safety profile. Aripiprazole was approved by the Food and Drug Administration on November 15, 2002 for the treatment of schizophrenia. This is also approved for the treatment of acute manic and mixed episodes associated with bipolar disorders.

PHARMACOLOGY

Aripiprazole is a quinolinone derivative. Its Chemical name is 7-[4-{4-(2, 3-dichlorophenyl)-1-piperazinyl}butoxy]-3, 4-dihydrocarbostyril. The empirical formula is $C_{23}H_{27}C_{12}N_3O_2$ and its molecular weight is 448.38. Aripiprazole acts as a dopamine system stabilizer, partial agonist at the D_2 and 5-HT_{1A} receptors and is an antagonist at $5HT_{2A}$ receptors. [2-5] It acts like a D_2 antagonist during hyper-dopaminergic activity and D_2 agonist during hypo-dopaminergic activity. Moreover, aripiprazole preserves normal dopamine activity at nigrostriatal and tuberoinfundibular dopaminergic pathways, thereby causing minimal EPS side effects and hyperprolactinemia. [6] In addition, aripiprazole's partial agonist effect at $5HT_{1A}$ receptors and its antagonist activity at $5HT_{2A}$ receptors may improve negative symptoms and cognitive function in schizophrenia.[1,7]

Aripiprazole is well absorbed with peak plasma concentration occurring within 3 to 5 hours. The oral bioavailability is 87%. The mean elimination half-life is about 75 hours for aripiprazole and 94 hours for its active metabolite (dehydro-aripiprazole). The parent drug represents a greater proportion of the drug exposure (60%) in plasma than its active metabolite, dehydro-aripiprazole. At doses of 5-30 mg/day, aripiprazole shows linear and dose proportional pharmacokinetics.[8] Aripiprazole and dehydro-aripiprazole are more than 99% bound to serum proteins (mainly albumin) at therapeutic concentration.[9] Clinical drug-drug interaction studies have not shown an effect of aripiprazole at dose of 10-30 mg/day on the pharmacokinetics of cytochrome isoenzymes CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2C19 substrates.[10] Drugs that induce CYP3A4 could cause an increase in aripiprazole clearance and lower plasma levels. Inhibitors of CYP3A4 (e.g., ketaconazole) or CYP2D6 (e.g., quinidine, fluoxetine or paroxetine) can inhibit aripiprazole elimination.

PRE-CLINICAL DEVELOPMENT

The discovery and characterization of dopamine in the mammalian brain earned Dr. Arvid Carlsson the Nobel Prize in 2000. Along with his many insights about dopamine pharmacology, came his proposal of the existence and critical role of dopamine autoreceptors in the overall regulation of dopamine-mediated neurotransmission. [11] Aripiprazole doesn't cause an upregulation of D_2 receptors or an increase in expression of the c-fos mRNA in the striatum. The mechanism of action of aripiprazole differentiates it from both typical and atypical antipsychotics and hence, may provide important leads for pharmacotherapy of schizophrenia and other psychotic disorders. [12] Aripiprazole displays properties of an agonist and antagonist in animal models. In a study conducted by Burris et al [2] which examined the interactions of aripiprazole with a single population of human D_2 receptors In membranes prepared from Chinese hamster ovary cells that express recombinant dopaminergic receptors, aripiprazole bound with high affinity to both the G-protein-coupled and uncoupled states of receptors. Results of this study supported the identification of aripiprazole as a dopamine-serotonin system stabilizer.

CLINICAL DEVELOPMENT

i) COMPARISON WITH TYPICAL ANTIPSYCHOTIC

A number of clinical trials were conducted to compare the efficacy of aripiprazole with other typical antipsychotics. The results were comparable on various efficacy parameters. Both short-term and long-term clinical trials have provided evidence that aripiprazole is effective in the treatment of schizophrenia. In a short term trial conducted by Kane et al,[13] aripiprazole and haloperidol produced significant improvement on efficacy parameters. Aripiprazole was found to be safe and effective for positive and negative symptoms of schizophrenia. In patients with treatment resistant schizophrenia, Kane et al [7] conducted another clinical trial comparing aripiprazole with perphenazine. Patients were randomly assigned to aripiprazole (15-30mg/day) or perphenazine (8-64mg/day). In results, 27% of aripiprazole treated patients and 25% of perphenazine treated patients were responder after 6week. Perphenazine treated patients had a higher incidence of extrapyramidal syndrome and a higher rate of elevated prolactin levels than aripiprazole (57.7% vs. 4.4%). The quality of life score revealed better results in patients treated with aripiprazole. Mcquade et al [14] conducted a long term comparative study of aripiprazole (20-30mg/day) with haloperidol (7-10mg/day). Higher number of patients on aripiprazole completed study as compared to haloperidol (40% vs. 27%). Aripiprazole was found to be significantly more effective than haloperidol on negative (PANSS) and depressive symptoms (MADRS) in patients of schizophrenia.

ii) COMPARISON WITH ATYPICAL ANTIPSYCHOTICS

A number of clinical trials were conducted to compare the efficacy of aripiprazole with other atypical antipsychotics. Chrzanowski et al [15] compared the long-term efficacy and safety of aripiprazole with olanzapine in patients with either acute relapsing or chronic, stable schizophrenia. Efficacy improvements were similar between aripiprazole and Olanzapine group. Tandon and jibson [16] compared efficacy of first line atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole) in the treatment of schizophrenia or schizoaffective disorder. This study showed that all the first line atypical antipsychotics were similarly effective for overall psychotic symptoms and positive & negative symptoms of schizophrenia. In a long-term double-blind study of olanzapine with aripiprazole in schizophrenia, treatment groups didn't differ significantly in time to all-cause discontinuation rate (olanzapine, 42.7% vs. aripiprazole, 50.2%). Olanzapine treated patients had significantly longer time to efficacy-related discontinuation and a significantly lower efficacy-related discontinuation rate (olanzapine, 8.9%, vs. aripiprazole, 16.8%). Olanzapine treated patients had a significantly greater mean decrease in PANSS total score than did aripiprazole treated patients. [17] Kinon BJ et al [18] conducted a 5-day, randomized, double-blind trial of olanzapine versus aripiprazole for the treatment of agitation in acutely ill patients with schizophrenia. Significant improvements from baseline in PANSS-EC and secondary efficacy measures were seen for both olanzapine and aripiprazole. Taylor et al [19] conducted an open label, 26-week, multi-centre, randomized study comparing aripiprazole with olanzapine, quetiapine or risperidone in patients with schizophrenia. The authors reported that more respondents rated the aripiprazole medication as 'much better' compared with their previous medication (Olanzapine, quetiapine or risperidone).

iii) SWITCH STUDIES

A number of switch studies were also conducted to prescribe and shift the patients from multiple doses to monotherapy with aripiprazole. Casey et al [20] conducted a

short-term open-label study to investigate the efficacy, safety and tolerability of three dosing strategies for switching chronic, stable patients with schizophrenia from current oral antipsychotic monotherapy to once-daily oral aripiprazole. In this trial, the efficacy with aripiprazole was revealed with numerical improvements compared with baseline in all treatment groups. In another similar clinical trial, Medori et al [21] documented findings in 311 patients with chronic, stable schizophrenia or schizoaffective disorder who had received monotherapy with a typical (haloperidol or thioridazine) or atypical (risperidone or olanzapine) antipsychotic for 1 month. Patients were shifted to aripiprazole monotherapy. The efficacy results were similar across treatment groups. There were no differences in discontinuations due to adverse events across the treatment groups. Antipsychotic efficacy was maintained in all groups throughout the study and improvement was seen from baseline in PANSS total score, PANSS negative and PANSS positive subscale scores, and CGI-Improvement score. Decreases in EPS rating scores, weight, and serum prolactin levels were also associated with switching to aripiprazole.

iv) SAFETY AND TOLERABILITY

Majority of the clinical trials conducted across globe revealed that aripiprazole is safe and its tolerability profile is documented in many studies. Mcquard et al [22] conducted a study comparing weight change during treatment with olanzapine or aripiprazole in randomized double blind controlled trial. In this clinical trial, at the end of twenty six weeks, 37% of olanzapine treated patients have experienced significant weight gain compared with 14% of aripiprazole treated patients. In another trial, the authors reported that olanzapine treated patients had significant greater mean increases in weight and glucose and a significantly greater worsening on lipid parameters in comparison to aripiprazole. [17] Olanzapine treated patients reported more extrapyramidal symptoms (EPS)-related adverse events (18%) than aripiprazole-treated patients (10%). Changes in fasting glucose and lipid levels at endpoint favoured aripiprazole over olanzapine, with significant differences observed for total cholesterol, low and high density lipoproteins. [15]

In one randomized comparative study of olanzapine and aripiprazole, safety of aripirazole and olanzapine was evaluated. Mean changes from baseline in non-HDL-C levels were significantly different with olanzapine versus aripiprazole at weeks 26 and 52. it was concluded that long term aripiprazole treatment is associated with improvements in lipid profiles of schizophrenia patients versus no improvement or worsening during olanzapine treatment. [23] Newcomer et al [24] compared the metabolic effects of aripiprazole versus olanzapine in overweight persons with schizophrenia or schizoaffective disorder who were previously on olanzapine treatment. In total, 173 subjects were randomly assigned to receive aripiprazole or olanzapine for 16 weeks. At week 16, weight decreased significantly with aripiprazole versus olanzapine (-1.8 vs. +1.41 Kg). Significant differences in percentage change in triglyceride levels were observed with aripiprazole versus olanzapine at all time-points. In addition, significantly more subjects receiving aripiprazole had clinically relevant weight loss versus olanzapine (11.1 % vs. 2.6%), and a lower percentage of subjects receiving aripiprazole had clinically relevant weight gain (2.5% vs. 9.1%). This study concluded that a significant improvement in weights and lipids was observed during discontinuation of olanzapine and switch to aripiprazole treatment.

Sedation, weight gain, and metabolic syndrome may be lass problematic with aripiprazole than with some other second-generation antipsychotics. Akathisia may limit its utility in some patients. Perhaps because of partial agonist effects at dopamine receptors, nausea and vomiting can occur when aripiprazole is started. Tolerability may be enhanced in patients if aripiprazole is initiated at 15mg or lower doses for a few days before being increased to as much as 30mg per day. Somnolence and constipation may be encountered with aripiprazole.

ARIPIPRAZOLE IN BIPOLAR DISORDERS

A number of multicenter, double-blind, placebo controlled trials have established the efficacy of aripiprazole monotherapy in acute mania (Keck et al, 2003; Sachs et al 2006). [25, 26] In the clinical trial conducted by Keck et al, [25], patients in an acute manic or mixed episode were randomly assigned 30mg/day or placebo. Aripiprazole produced statistically significant mean improvements in total score on the Young Mania Rating Scale compared with the placebo (-8.2 versus -3.4, respectively) and produced a significantly higher response rate (40% versus 19%). The completion rate was significantly higher with aripiprazole than with placebo (42% versus 21%). Aripiprazole monotherapy appeared to have a broad spectrum of efficacy. Sachs et al. [26] conducted a 3-week placebo-controlled aripiprazole study in the treatment of acute manic or mixed episodes in patients with bipolar 1 disorder. Aripiprazole-treated patients demonstrated significantly greater improvement from baseline to endpoint in mean YMRS total scores compared with placebo-treated patients as early as Day 4

and sustained through week 3. A significantly higher response rate was observed in aripiprazole-treated patients (53% vs. 32% at endpoint). Aripiprazole produced significantly greater improvement from baseline on other efficacy assessments compared with placebo, including Clinical Global Impression-Bipolar Version Severity and Improvement scores.

CONCLUSION

Aripiprazole is the most balanced drugs with dopamine-serotonin stabilizing properties. Aripiprazole is equally effective in the treatment of schizophrenia as compare to typical and atypical antipsychotics. In majority of clinical trials aripiprazole has been compared with olanzapine. Olanzapine has similar efficacy as aripiprazole but more weight gain and deranged lipid profile is reported from olanzapine receipients. Aripiprazole has the low potential for the drug drug interactions. Aripiprazole has the better tolerability profile as compared to typical antipsychotics. Thus, aripiprazole is the favourable option with improved efficacy and tolerability profile in the patients with schizophrenia.

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Source of support/Conflicting Interest : nil

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