Aripiprazole: A New Antipsychotic Agent with a Unique Mechanism of Action

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INTRODUCTION

Although early antipsychotic agents, such as chlorpromazine (Thorazine®, GlaxoSmithKline) and haloperidol (Haldol®, Ortho-McNeil) showed great promise initially, their limitations became evident when extrapyramidal side effects were associated with their use. Subsequently, the novel atypical antipsychotics, such as clozapine (Clozaril®, Novartis), risperidone (Risperdal®, Janssen), olanzapine (Zyprexa®, Eli Lilly), quetiapine fumarate (Seroquel®, AstraZeneca), and ziprasidone (Geodon™, Pfizer), demonstrated fewer extrapyramidal side effects, thus providing an option for practitioners. However, patients taking these agents experienced various side effects, including weight gain, hyperglycemia, dyslipidemia, and, in certain cases, an increased QT interval.

Aripiprazole (Abilify™) is a new antipsychotic agent with a proposed unique mechanism of action. As a dopamine system stabilizer (DSS), it appears to be significantly better at regulating the positive and negative symptoms associated with schizophrenia than placebo and has shown to be as efficacious as risperidone and haloperidol in its response to those symptoms. After submitting a New Drug Application to the Food and Drug Administration (FDA) in October 2001,1 Bristol-Myers Squibb and Otsuka America Pharma, Inc., received approval in November 2002 to market aripiprazole.

PHARMACOLOGY

The brain normally stabilizes dopamine neurotransmission by attaining a balance between presynaptic and postsynaptic dopamine 2 (D2) receptors. The two systems work in conjunction, activating receptors in areas of the brain where dopamine concentrations are too low and inactivating receptors where they are too high. Presynaptic dopamine receptors that are responsible for controlling dopamine release are less sensitive than postsynaptic receptors in detecting dopamine levels.

Neurotransmission of dopamine continues until levels build sufficiently to stimulate the presynaptic receptors. This feedback mechanism inhibits the release of excessive dopamine.2 The goals of treatment, therefore, are to enhance understimulated dopamine neurons and to reduce the overactive neurons in the mesocortical areas of the brain while regulating normal physiological prolactin and motor functions.

The dopamine system stabilizer is unique: when dopaminergic activity is excessive, it reduces dopaminergic transmission. When dopamine levels are deficient, the system also enhances activity but does so only until dopamine is within normal parameters, thereby preventing hyperactivity of dopamine neurons, which can result in psychosis. The restoration of dopamine activity in the brain’s cortical regions regulates cognitive and negative symptoms as well as prolactin and motor activity.3

Because aripiprazole possesses both stimulatory and inhibitory properties, it has been referred to as a partial agonist. This possibly misleading term can cause clinicians to believe that the efficacy of aripiprazole is incomplete. In a study by Burris et al.,4 aripiprazole’s interactions with human dopamine 2-like (D2L) receptors were evaluated to further clarify its pharmacological properties. In membranes prepared from Chinese hamster ovary (CHO) cells that expressed recombinant D2L receptors, aripiprazole bound the D2 receptor with high affinity. Consistent with the expected effects of a partial agonist, increasing concentrations of aripiprazole blocked the action of dopamine with maximal blockade equal to the agonist effect of aripiprazole alone.

Inoue et al.5 analyzed the effects of aripiprazole on the prolactin secretion of 6-day-old anterior pituitary cell cultures. Their results suggested that aripiprazole regulates dopaminergic transmission by exerting D2 agonism or antagonism as a function of high or low receptor availability.

Although we know that a relationship between antipsychotic activity and dopamine receptor binding ability exists, recent attention has targeted the 5-hydroxytryptamine (5-HT1A) receptor as an option in treating antipsychotic behavior.6 Aripiprazole was also observed to have potent partial agonist activity at human 5-HT1A,7 a finding that might lend itself to the overall efficacy against symptoms of schizophrenia.

PHARMACOKINETICS

To date, no therapeutic drug concentrations of aripiprazole have been established. Although quantitative data are limited with respect to the drug’s bioavailability, Yokoi et al.8 reported that administration of aripiprazole for 14 days in 15 males, in doses of 0.5, 1, 2, 10, and 30 mg/day, resulted in dose-dependent receptor occupancy between 40% and 95%. The investigators found that it was possible to obtain an adequate occupancy and that the data might be useful at predicting appropriate therapeutic doses.

Lawler et al.9 examined aripiprazole and its interaction with receptor subtypes
reported on liver metabolism but did not clarify the extent of metabolism. The major metabolite, as observed from in vivo animal data, was hydroxyaripiprazole, but the authors did not establish the extent of its activity.

**Efficacy**

Petrie et al.\(^{10}\) studied the basic efficacy and tolerability of aripiprazole in phase II trials. Two double-blind, four-week studies enrolled 410 hospitalized patients with acutely relapsing schizophrenia. In the first study, aripiprazole was titrated to 30 mg over 13 days; in the second study, patients received a fixed dose of 2, 10, or 30 mg/day from the start. From both studies, 143 patients participated in the ongoing, follow-up, open-label outpatient trial in which all patients received a maximum dose of 30 mg/day.

The fixed-dose study showed that 30 mg could be given without titration. That dose showed a significant effect on all assessments, including the Positive and Negative Syndrome Scale (PANSS)–Negative score, starting at one-week evaluations. The 2- and 10-mg doses showed an effect on many assessment findings, but not all (and not on the PANSS-Negative), starting at week two or week three. All doses were well tolerated; no weight gain, elevated prolactin levels, neurological or cardiovascular effects, sedation, or anticholinergic reactions were observed.

Kane et al.\(^{11}\) compared haloperidol and placebo with aripiprazole in a phase III double-blind, four-week clinical trial. Two fixed doses of aripiprazole (15 and 30 mg), haloperidol (10 mg), and placebo were administered to more than 400 patients with a diagnosis of acute relapsing schizophrenia or schizoaffective disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The efficacy of both doses of aripiprazole and haloperidol was significantly superior to that of placebo (a change in PANSS-Total, Brief Psychiatric Rating Scale [BPRS]-Total, at last observation carried forward; \(P < .01\)). However, the responder analysis (a 30% decrease from the baseline in PANSS-Total at the last visit) indicated that both doses of aripiprazole worked significantly better than placebo (\(P < .05\)), whereas the response to haloperidol was not significantly different from the response to placebo (\(P < .1\)).

Aripiprazole was well tolerated, and the number of patients who discontinued the medication because of adverse effects was lower than the number taking placebo or haloperidol. The investigators observed no clinically meaningful increase in QTC prolongation in patients receiving aripiprazole. Extrapyramidal symptoms in patients taking aripiprazole did not differ in patients taking placebo.

Kern et al.\(^{12}\) compared aripiprazole with olanzapine in a multicenter, randomized, open-label clinical trial to test its efficacy at remediating neurocognitive deficits. The authors observed a sample of 256 chronic, stable outpatients with a diagnosis of schizophrenia or schizoaffective disorder for 26 weeks. Patients were randomly assigned to receive one of two treatments: 30 mg/day of aripiprazole or 15 mg/day of olanzapine. After administering a series of tests to measure verbal fluency, executive functioning, verbal and visual secondary memory, working memory, vigilance, and manual dexterity, the authors suggested that aripiprazole might help ameliorate neurocognitive deficits associated with schizophrenia.

**Adverse Reactions**

Although minimal side effects from aripiprazole have been reported, complete clinical data have not yet been established. In a 52-week study reported by Bristol-Myers Squibb,\(^{13}\) 1,294 patients with schizophrenia were evaluated to establish efficacy, safety, and tolerability. Patients taking aripiprazole experienced significantly fewer extrapyramidal symptoms than patients taking haloperidol. The most commonly reported adverse drug events associated with aripiprazole in this study were insomnia, psychosis, anxiety, and akathisia. The incidence of insomnia, psychosis, and anxiety was similar to that with haloperidol, whereas the incidence of akathisia was considerably less with aripiprazole than with haloperidol (\(P < .001\)).

In a 26-week study by the manufacturer,\(^{13}\) aripiprazole was compared with placebo for efficacy and safety in 310 patients. No significant differences were found in the incidence of extrapyramidal side effects or weight gain. The three most commonly reported symptoms associated with aripiprazole were insomnia, anxiety, and headache, with incidence rates similar to those for placebo.

A study presented at the 155th Annual Meeting of the American Psychiatric Association, held in Philadelphia in May 2002, described how patients who were switched from olanzapine to aripiprazole therapy demonstrated a statistically significant weight loss of 2.03 kg (\(P < .001\)) along with a decrease in prolactin levels and an improvement in extrapyramidal side effects. Patients who were switched from risperidone to aripiprazole therapy showed statistically significant decreases in prolactin levels (\(P < .001\)), with reductions in weight and in extrapyramidal symptoms.\(^{14}\) The decreased incidence of side effects can be associated with aripiprazole’s lack of affinity for histaminergic, alpha-adrenergic, and muscarinic receptors.

**Precautions and Contraindications**

Although no contraindications or precautions have been clearly established for aripiprazole, caution must be exercised for patients who are taking antipsychotic medications. Because of the limited data available, pregnant patients and patients with cardiovascular disease, hypovolemia, Parkinson’s disease, or renal or hepatic insufficiency should be evaluated on an individual basis.

**Drug Interactions**

Both the CYP2D6 and CYP3A4 enzymes are responsible for aripiprazole metabolism. Agents that induce the CYP3A4 enzyme (e.g., carbamazepine) can increase aripiprazole clearance. Medications that inhibit the CYP3A4 enzyme (e.g., ketoconazole) or the CYP2D6 enzyme (e.g., fluoxetine) may hinder aripiprazole elimination.\(^{15}\) Certain combinations, such as the concomitant use of central nervous system depressants and alcohol, should be monitored. Aripiprazole should be prescribed with caution for patients who are at risk for torsades des pointes from their use of QT-prolonging agents, such as antiarrhythmic agents and antidepressants.

**Conclusion**

Aripiprazole, the first in a new class of antipsychotic medications, shows...
promise because of its unique mechanism of potent D2 partial agonist activity, coupled with its 5-HT1A agonist activity. Although the facts are still emerging, most trials have indicated superior performance with aripiprazole in terms of its comparable efficacy and benefits in producing fewer extrapyramidal side effects. One of the most challenging aspects of treating patients with schizophrenia is the problem of compliance. An agent that offers a reduction in adverse effects and that has an efficacy similar to that of other treatments might result in increased long-term adherence. Should aripiprazole live up to expectations, great strides will be made in the treatment of mental illness.

REFERENCES