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New Investigators

What makes aripiprazole the 'different' antipsychotic

Off-label use of 'dopamine stabilizer' requires caution

Mahendra T. Bhati, MD
Neuropsychiatry fellow
Department of psychiatry
University of Pennsylvania
Philadelphia, PA

Aripiprazole, the first FDA-approved partial dopamine agonist, causes few side effects when used to treat schizophrenia or acute bipolar mania. This relatively safe profile in approved uses has led clinicians to try aripiprazole for off-label uses as well, though evidence of the drug's efficacy and safety in other psychiatric conditions is limited (*Box 1, page 52*).[1-7] Because this practice may involve unknown risks, this article:

- reviews aripiprazole's role in correcting dopaminergic dysfunction in patients with schizophrenia
- cites adverse effects reported with aripiprazole use and discusses concerns about its off-label use.

DOPAMINE AND SCHIZOPHRENIA

Dopamine neurons arise from two major nuclei in the mesencephalon (midbrain): the substantia nigra and ventral tegmental area (VTA). Neurons

New insights on psychotropic drug safety and side effects

This paper by Dr. Mahendra T. Bhati was entered in the 2005 Promising New Investigators competition sponsored by the Neuroleptic Malignant Syndrome Information Service (NMSIS). The theme of this year's scholarly papers was "New insights on psychotropic drug safety and side effects."

Current Psychiatry is honored to publish this peer-reviewed, evidence-based article on a clinically important topic for practicing psychiatrists.

NMSIS is dedicated to reducing morbidity and mortality of NMS by improving medical and psychiatric care of patients with heat-related disorders; providing support information for medical professionals, patients and families; and improving scientific understanding of these conditions through research.

Box 1

Off-label aripiprazole: The unknowns

Aripiprazole shows clear efficacy for treating acute mania and schizophrenia's negative and positive symptoms, but its effectiveness and safety in other psychiatric illnesses is unknown. Even so, it is being used to treat psychotic unipolar and bipolar depression, attention-deficit/hyperactivity disorder, oppositional defiant disorder, and pervasive developmental disorders in children and adults.

Dopamine differences. Do not assume that aripiprazole's safety and effectiveness in treating schizophrenia translates to other psychiatric conditions. Dopamine dysfunction patterns differ in persons with and without schizophrenia; therefore, aripiprazole's regional and functional selectivity at dopamine receptors—and treatment response and tolerability—is also likely to differ.

Antipsychotic differences. Aripiprazole is unlike other psychotropics and cannot be assumed to have similar therapeutic effects. The agent's dopamine agonist and antagonist properties hinge on regional dopamine concentrations as well as the drug itself.

Dopaminergic risks in combination. Numerous drugs modulate dopamine function, and switching and combining drugs places patients at unknown risk of dopaminergic side effects with aripiprazole. Adding an antagonist or a low-dose antagonist combination with aripiprazole may increase competition for dopamine receptors and modify its intrinsic activity, depending on the antagonist dosage and regional dopamine concentrations.

Source: References 1-7

from the substantia nigra extend to the basal ganglia via the mesostriatal (nigrostriatal) pathway, which influences extrapyramidal motor function. The VTA sends dopaminergic neurons through mesolimbic and mesocortical pathways.

The basic limbic system includes the cingulate and orbitofrontal gyri, hippocampus, hypothalamus, thalamus, amygdala, medial temporal cortex, and the periaqueductal gray. This system controls emotion, episodic memory, pain, and primitive behaviors such as eating, fighting, sexual desire, and grooming.[8] The limbic system is surrounded by cortex, where higher-order sensory, cognitive, and motor processes occur. The VTA links limbic and cortical functions via dopamine.

The tuberoinfundibular pathway, another clinically important dopaminergic route, projects from the hypothalamus to the anterior pituitary gland and regulates prolactin secretion.

Functional dopamine neurotransmission abnormalities in schizophrenia are generally characterized by region, with:

- excessive mesolimbic pathway activity resulting in positive symptoms such as delusions and hallucinations
- mesocortical projection deficits resulting in cognitive and negative symptoms such as impaired memory and attention, emotional blunting, alogia, avolition, and anhedonia.

Dopamine function abnormalities in schizophrenia occur in:

- projections from the substantia nigra to the caudate and putamen in the basal ganglia
- mesolimbic connections to the anterior cingulate, hippocampus, and parahippocampus
- mesocortical projections to the prefrontal cortex.

These dysfunctions contribute to abnormal motor function, perception, attention, memory, volition, emotion, and executive function.[9]

WHY ARIPIPRAZOLE WAS CREATED

Differences in regional dopamine function and observations of dopamine agonists' therapeutic effects in schizophrenia[10] led to development of partial dopamine agonists such as aripiprazole (*Box 2*).[11,12]

Aripiprazole and the investigational agent bifeprunox have complex pharmacologic actions involving numerous neurotransmitters—dopamine, serotonin, and histamine—but are believed to be principally partial agonists at pre- and postsynaptic dopamine receptors. Specifically, aripiprazole decreases hyperdopaminergic states while preserving dopamine function by partial agonism and decreased stimulation of presynaptic regulatory autoreceptors.[5]

The FDA approved aripiprazole for treating schizophrenia in 2002 and acute bipolar mania in 2004. A dihydroquinolone unrelated to other antipsychotics, it has an active partial agonist metabolite (dehydro-aripiprazole), high affinity for D2 receptors (*Figure 1, page 54*), and partial agonism at dopamine and serotonin receptors.[13]

Phase III trials are in progress for bifeprunox, a partial dopamine agonist/antagonist and serotonin receptor agonist being investigated for schizophrenia. An FDA decision on its approvability is expected in 2007.

Aripiprazole has approximately 30% intrinsic dopaminergic activity, estimated from studies showing a low incidence of extrapyramidal symptoms (EPS) with dosages up to 30 mg and PET studies showing a therapeutic range of postsynaptic D2 receptor occupancy of 80% to 95%.[14] This small intrinsic activity limits excessive stimulation and dopamine receptor blockade.[11] It also limits down-regulation of regulatory dopamine autoreceptors and preserves dopaminergic function in pre- and postsynaptic neurons.

The therapeutic window for dopamine receptor agonists (DA) and serotonin-dopamine receptor agonists (SDA) used in schizophrenia is 60% to 80% D2 receptor occupancy in mesostriatal neurons. D2 receptor occupancy and antagonism >80% significantly increases risk of EPS.[15] Excessive dosing of high-potency antipsychotics with strong postsynaptic dopamine receptor affinity carries the highest risk of hypodopaminergic side effects, such as cognitive impairment, worsening of negative symptoms, akathisia, Parkinsonism, and hyperprolactinemia.

Aripiprazole's intrinsic activity allows for higher D2 receptor occupancy with fewer side effects associated with full dopamine receptor antagonism. Clinical implications of this profile are unknown. Dopamine's role in schizophrenia's pathophysiology is inferred from knowledge that all effective antipsychotics offer some postsynaptic D2 receptor blockade.

Box 2

What makes partial dopamine agonists 'different' antipsychotics

Conventional dopamine receptor agonists (DAs) such as haloperidol and the newer serotonin-dopamine receptor agonists (SDAs) modeled after clozapine are thought to exert clinical effect by blocking D2 and D3 receptors. By contrast, partial dopamine agonists are agonists or antagonists, depending on cell-specific, synaptic dopamine concentrations. DAs and SDAs are competitive, full antagonists at pre- and postsynaptic dopamine receptors, whereas partial dopamine agonists are:

- agonists at presynaptic regulatory autoreceptors and in hypodopaminergic (mesocortical) synapses
- antagonists with small intrinsic activity in hyperdopaminergic (mesolimbic) synapses. Intrinsic activity is a compound's degree of agonism in proportion to full agonism.

'Dopamine stabilizers.' Because of this combination of high-affinity receptor antagonism with preserved intrinsic activity, some call partial dopamine agonists "dopamine stabilizers."

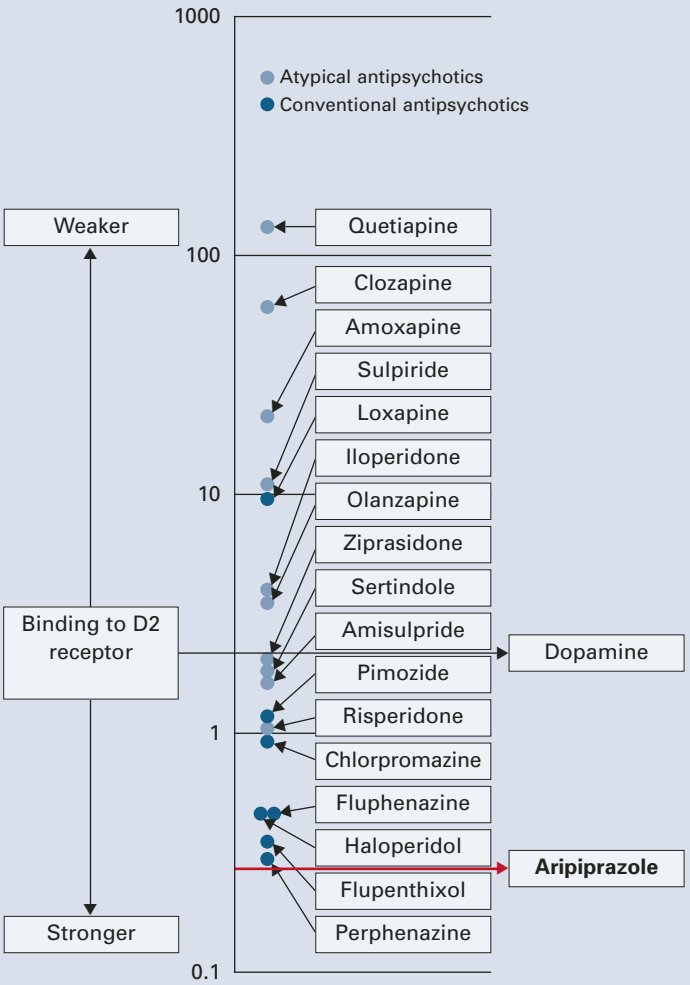
Source: References 11, 12

SIDE EFFECTS

Evidence shows fewer side effects with aripiprazole when used to treat schizophrenia and

Figure

Antipsychotics' D2 receptor binding affinities



Aripiprazole shows strong D2 receptor binding when compared with other antipsychotics.

schizoaffective disorder compared with DAs such as haloperidol and SDAs such as risperidone.[1,2,4]

Dosage-dependent somnolence occurs with aripiprazole; the most common side effects include headache, agitation, anxiety, and insomnia (24.5%, 34.6%, 24%, and 18.6%, respectively).[2]

A 10-week, placebo-controlled study using aripiprazole, 2 to 15 mg/d, to treat psychosis in Alzheimer's dementia showed significantly increased risk of somnolence, accidental injury, and bronchitis (likely caused by aspiration).[16]

In placebo-controlled trials, aripiprazole, 2 to 30 mg/d, did not increase risk of cardiac, lipid, or prolactin-related side effects[2] but showed increased risk of:

- tremor when used at 15 mg/d for up to 26 weeks in chronic schizophrenia, (9% incidence vs 1% with placebo)[17]
- akathisia when used at mean dosages of 27.9 mg/d to treat acute bipolar mania (11% incidence vs 2% with placebo).[3] Aripiprazole also increased akathisia incidence in normal subjects.[18]

Risk of tardive dyskinesia or hyperglycemia-related adverse events with aripiprazole are unknown. Studies report weight gain of <1 kg (<2.2 lbs) in patients taking aripiprazole, 2 to 30 mg/d. One study found that patients switched from DA and SDA antipsychotics to aripiprazole, 30 mg/d, lost on average 1.5 kg (3.2 lbs) across 8 weeks.[19]

Determining neuroleptic malignant syndrome risk with aripiprazole is difficult; two cases were reported in the premarketing sample.[16] One animal study showed diminished catalepsy with chronic aripiprazole use, in contrast to persistent catalepsy with haloperidol.[20]

A Medline search for aripiprazole in February 2005 found several reports of treatment-emergent side effects, including:

- 3 reports of worsening agitation or psychosis[21-23]
- 2 reports of EPS[24, 25]
- 1 report of excessive somnolence in a child.[26]

Adverse effects are probably underrepresented.

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Related resources

- Lieberman, J. Aripiprazole. In: Schatzberg, A, Nemeroff, C (eds.) *Textbook of Psychopharmacology*. Washington DC: American Psychiatric Publishing, 2004:487-494.
- FDA Center for Drug Evaluation and Research. http://www.fda.gov/cder/foi/nda/2002/21-436_Abilify.htm
- Medline Plus Drug Information. http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a603012.html

DRUG BRAND NAMES

Aripiprazole • Abilify
Clozapine • Clozaril
Haloperidol • Haldol
Risperidone • Risperdal
Trazodone • Desyrel
Sertraline • Zoloft
Venlafaxine • Effexor

DISCLOSURE

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Clinical deterioration and adverse effects were reported after starting, switching to, or combining aripiprazole with other antipsychotics or serotonergic agents (trazodone, sertraline, or venlafaxine).[27, 28]

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Bottom Line

Aripiprazole is being used off-label to treat a range of psychiatric disorders in adults and children, but its unique profile makes predicting treatment response and tolerability difficult. More research is needed to determine its role beyond treating schizophrenia and acute bipolar mania.