Mr. N, age 29, presents to the emergency department at the urging of his family because of poor self-care, bizarre behavior, and disturbed sleep. He first experienced psychiatric symptoms 10 years ago after his mother died. He became dysphoric and paranoid, displaying bizarre responses and behaviors with poor self-care and a gradual functional decline. He has been taking sertraline, 100 mg/d, for 10 years.

Upon arrival at the hospital’s inpatient unit, Mr. N is unkempt, oddly related, and paranoid. His affect is constricted. Mr. N displays thought blocking and possibly is responding to internal stimuli. Sertraline is continued and haloperidol, 1 mg/d, is initiated. For the next 2 weeks, Mr. N continues to be oddly related, irritable, and paranoid, and experiences disturbed sleep and thought blocking. After an episode of impulsive aggression, the treatment team initiates aripiprazole, which is titrated to 30 mg/d for 1 week. Mr. N’s clinical status worsens; he is menacing toward other patients and his thinking is more disorganized, with loose associations and ideas of reference. He requires 4 injections of IM haloperidol, 5 mg, and several visits to the seclusion room over the next week. Haloperidol is increased to 30 mg/d over the next 10 days, then aripiprazole is discontinued because of a putative drug interaction with haloperidol. Following the medication changes Mr. N demonstrates better behavioral control, but still is grossly psychotic. While awaiting transfer to a state hospital, Mr. N receives a trial of olanzapine, 20 to 40 mg/d, for 2 weeks without significant benefit.

Several clinical trials demonstrate a significant reduction in intensity of psychotic symptoms with aripiprazole, which has a unique mechanism of action. However, since its FDA approval in 2002, several case reports have described treatment-emergent psychiatric symptoms associated with aripiprazole initiation. Over the past 40 years, reports of worsening psychosis associated with antipsychotics have been limited to patients with schizophrenia who were taking high dosages or who had high plasma concentrations, when anticholinergic delirium may have explained increased psychotic symptoms.

How can a drug effectively treat psychotic symptoms and occasionally worsen Is there a link between aripiprazole and treatment-emergent psychosis?

James J. Gugger, PharmD, BCPP, Courtney L. Tam, PharmD, and Charles R. Ashby, Jr, PhD

Practice Points

- Aripiprazole may interact preferentially with distinct conformations of the D2 receptor, leading to a spectrum of pharmacologic effects, including acting as a full agonist, partial agonist, or antagonist.

- Clinical predictors of aripiprazole-associated worsening of psychosis include low baseline level of psychopathology and previous treatment with high-dose antipsychotics.

- Rapid transition from a medication with significant anticholinergic properties to 1 without these properties may result in symptoms of activation, including restlessness, insomnia, and anxiety, which can be mistaken for worsening psychosis.

- Akathisia, a common adverse effect of aripiprazole, may masquerade as treatment-emergent worsening of psychotic symptoms.
them? In this article, we discuss the relevant pharmacology and clinical literature on aripiprazole and try to make sense of this apparent paradox.

**Unique pharmacologic profile**

Antipsychotics have been reported to be either neutral antagonists or inverse agonists at the D2 receptor, based on *in vitro* data. Aripiprazole and its main metabolite, dehydroaripiprazole, originally were described as partial agonists at D2 dopamine receptors. However, it appears aripiprazole’s pharmacologic action is better explained by the concept of functional selectivity. Aripiprazole may interact preferentially with distinct conformations of the D2 receptor, leading to a spectrum of pharmacologic effects, including acting as a full agonist, partial agonist, or antagonistic.

Researchers have hypothesized that the pathophysiology of schizophrenia may, in part, be caused by dysfunction of mesocorticolimbic dopaminergic neurons characterized by an enhanced sensitivity of postsynaptic D2 receptors and increased sensitivity to dopaminergic drugs. In addition, chronic treatment with a D2 receptor antagonist is associated with increases in postsynaptic dopamine receptor density (ie, an increase in receptor reserve). Upregulation of D2 receptors may explain several features seen in patients chronically treated with antipsychotics, including tardive dyskinesia and rapid psychotic relapse after discontinuing an antipsychotic (supersensitivity psychosis). Because chronic antipsychotic treatment leads to high postsynaptic receptor reserve, aripiprazole initiation may produce overactivation of D2 receptors, which might worsen a patient’s condition. In *vitro* data and clinical observations indicate that aripiprazole has intrinsic efficacy at D2 receptors, as do clinical observations, such as:

- Its propensity to reduce serum prolactin
- A decreased likelihood of producing extrapyramidal side effects despite >80% occupancy of D2 receptors
- Case reports documenting aripiprazole-associated mania, improvement of risperidone-associated cognitive impairment, and pathologic gambling.

Emergence or worsening of psychotic symptoms or a marginal antipsychotic effect may occur if aripiprazole is indeed a postsynaptic D2 receptor agonist. An individual patient’s outcome likely would depend on his or her sensitivity to psychosis and concurrent or previous exposure to a D2 receptor antagonist. For example, stimulation of postsynaptic D2 receptors may be further augmented if the dosage of the previous antipsychotic was reduced or withdrawn before initiating aripiprazole because additional receptors would be available for interaction with aripiprazole.

**Case reports**

A literature review revealed 23 reports of treatment-emergent psychosis associated with aripiprazole initiation (*Table, page 56-57*). The mean age of the patients was 47 (range: 17 to 69) and 57% were men. Most patients (87%) were diagnosed with a schizophrenia-spectrum illness before aripiprazole initiation. Most (57%) had mild, stable, or no psychotic symptoms before aripiprazole initiation. Most were receiving relatively high doses of antipsychotics (average chlorpromazine equivalents [CPZE]: 648 mg/d) before aripiprazole initiation. This medication was either decreased or discontinued in 70% of patients. Emergence or worsening of psychotic symptoms included agitation, aggressive behavior, and increased psychomotor activity. However, akathisia evaluation was described in only 2 reports: 1 author identified akathisia symptoms, but attributed them to a concomitant antipsychotic (fluphenazine) and the other report specifically excluded the possibility of akathisia. Two systematic studies have attempted to establish risk factors for aripiprazole-associated worsening psychosis (*Box*).

In our literature review, the mean final dose of aripiprazole was 21.5 mg/d (range: 2 to 60 mg/d). In the cases describing subsequent treatment, all but 1 patient were switched to another antipsychotic, including 2 whose psychotic symptoms
stabilized with continuation of aripiprazole and addition of a second antipsychotic. Interestingly, in the case reported by Adan-Manes et al, initial treatment with aripiprazole monotherapy was efficacious, but a subsequent trial of adjunctive aripiprazole resulted in worsening psychosis.

**Other potential explanations**

Aripiprazole’s manufacturer reported the incidence of psychosis-related adverse events in an analysis of 9 randomized schizophrenia trials. The rates of psychosis-related adverse events ranged from 0.6% to 18%, but there was no apparent relationship to study design or method of transitioning to aripiprazole. Rates of psychosis-related adverse events were similar between aripiprazole and the control group (placebo in 3 studies, another antipsychotic in 2 studies).

Emergence or worsening of psychotic symptoms temporally associated with aripiprazole initiation does not necessarily imply causation. As in Mr. N’s case, it is not always possible to determine whether worsening psychosis is the natural disease course or a treatment effect. In addition, it is not possible to differentiate lack of efficacy from a true propensity for aripiprazole to worsen psychosis.

It also is conceivable discontinuation or dosage reduction of a previous antipsychotic would worsen psychotic symptoms or cause side effects. When significant changes in psychopathology or side effects develop during the transition from 1 antipsychotic to another, it is difficult to determine etiology. Specifically, rapid transition from a medication with significant anticholinergic and antihistaminic properties—such as quetiapine or olanzapine—to 1 without these properties—such as aripiprazole—may result in symptoms of activation, including restlessness, insomnia, and anxiety. Consequently, these symptoms could be mistaken for worsening psychosis. Only 1 patient in this series was reported to abruptly discontinue an antipsychotic with significant anticholinergic properties (clozapine) before initiating aripiprazole. Studies by Takeuchi et al and Pae et al did not report the relative baseline use of antipsychotic medication with anticholinergic properties.

In a pooled analysis of treatment-emergent adverse events in 5 randomized clinical trials of patients receiving aripiprazole for acute relapse of schizophrenia, the incidence of akathisia was 10%, although it is not clear if this is a dose-related adverse effect because akathisia may be confused for worsening psychosis. It is possible akathisia was mistakenly identified as worsening psychotic symptoms in Mr. N’s case, as well as several reports from our literature review.

Covert akathisia is unlikely to explain worsening psychopathology observed in...
### Case reports: Treatment-emergent psychosis associated with aripiprazole

<table>
<thead>
<tr>
<th>Study</th>
<th>Age, sex</th>
<th>Diagnosis</th>
<th>Before aripiprazole initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiu et al, 2011a</td>
<td>39, M</td>
<td>Schizophrenia</td>
<td>Psychiatically stable, tardive dystonia</td>
</tr>
<tr>
<td>Ekinci et al, 2010b</td>
<td>17, M</td>
<td>ADHD</td>
<td>Inattention and impulsive aggression</td>
</tr>
<tr>
<td>Selvaraj et al, 2010c</td>
<td>49, F</td>
<td>Chronic depression</td>
<td>Depressive symptoms, suicidal ideation</td>
</tr>
<tr>
<td>Adan-Manes et al, 2009d</td>
<td>23, M</td>
<td>Schizophrenia</td>
<td>No psychotic symptoms</td>
</tr>
<tr>
<td>Cho et al, 2009e</td>
<td>45, F</td>
<td>Schizophrenia</td>
<td>Persistent psychotic symptoms, new onset diabetes with acute ketoacidosis</td>
</tr>
<tr>
<td>Ahuja et al, 2007f</td>
<td>35, F</td>
<td>Schizoaffective disorder</td>
<td>Stable before medication change</td>
</tr>
<tr>
<td>Lea et al, 2007g</td>
<td>57, M</td>
<td>Schizophrenia</td>
<td>Persistent psychotic symptoms, treatment resistance, recent recovery from NMS</td>
</tr>
<tr>
<td>Lea et al, 2007g</td>
<td>49, M</td>
<td>Schizoaffective disorder</td>
<td>Delusions, verbal aggression, substance abuse, HCV</td>
</tr>
<tr>
<td>Lea et al, 2007g</td>
<td>60, M</td>
<td>Schizophrenia</td>
<td>Delusions, labile mood, aggression</td>
</tr>
<tr>
<td>Raja, 2007h</td>
<td>30, M</td>
<td>Schizoaffective disorder</td>
<td>Negative symptoms, otherwise stable, recent citalopram discontinuation</td>
</tr>
<tr>
<td>Raja, 2007h</td>
<td>69, F</td>
<td>Bipolar disorder</td>
<td>History of multiple relapses; presented with tremor, akathisia, weight gain</td>
</tr>
<tr>
<td>Raja, 2007h</td>
<td>59, F</td>
<td>Schizophrenia</td>
<td>Negative symptoms, otherwise stable</td>
</tr>
<tr>
<td>Thone, 2007i</td>
<td>31, M</td>
<td>Schizophrenia</td>
<td>Confusion, agitation, delusions worsened with aripiprazole dose increase</td>
</tr>
<tr>
<td>Glick et al, 2006f</td>
<td>55, F</td>
<td>Schizophrenia</td>
<td>Stable before medication change</td>
</tr>
<tr>
<td>Glick et al, 2006f</td>
<td>52, M</td>
<td>Schizophrenia</td>
<td>Negative symptoms</td>
</tr>
<tr>
<td>Barnas et al, 2005k</td>
<td>57, F</td>
<td>Schizoaffective disorder</td>
<td>Stable before medication change</td>
</tr>
<tr>
<td>DeQuardo, 2004l</td>
<td>54, M</td>
<td>Schizophrenia</td>
<td>History of aggression, residual paranoia, severe EPS</td>
</tr>
<tr>
<td>DeQuardo, 2004l</td>
<td>51, M</td>
<td>Schizophrenia</td>
<td>History of aggression, persistent psychotic symptoms, treatment resistance</td>
</tr>
<tr>
<td>Ramaswamy et al, 2004m</td>
<td>43, F</td>
<td>Schizoaffective disorder</td>
<td>Psychiatically stable, multiple medication changes, including substituting carbamazepine for valproic acid</td>
</tr>
<tr>
<td>Ramaswamy et al, 2004m</td>
<td>57, F</td>
<td>Schizoaffective disorder</td>
<td>History of multiple hospitalizations, but stable before medication change</td>
</tr>
<tr>
<td>Ramaswamy et al, 2004m</td>
<td>67, F</td>
<td>Schizophrenia</td>
<td>Remote hospitalizations, recent worsened psychosis</td>
</tr>
<tr>
<td>Ramaswamy et al, 2004m</td>
<td>46, M</td>
<td>Schizophrenia</td>
<td>Persistent delusions while receiving risperidone, TD</td>
</tr>
<tr>
<td>Reeves et al, 2004c</td>
<td>50, M</td>
<td>Schizoaffective disorder</td>
<td>Relatively stable with nortriptyline, hallucinations</td>
</tr>
</tbody>
</table>

**Clinical Point**

It is not possible to differentiate lack of efficacy from a true propensity for aripiprazole to worsen psychotic symptoms.
<table>
<thead>
<tr>
<th>Pre-ariprazole treatment</th>
<th>Aripiprazole dose</th>
<th>Concomitant psychotropic treatment</th>
<th>Subsequent treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine, 300 mg/d</td>
<td>10 mg/d</td>
<td>Valproic acid, 1,000 mg/d, clonazepam, 2 mg/d, mephenoxalol, 800 mg/d</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Tapered and discontinued risperidone, 2.5 mg/d</td>
<td>5 mg/d</td>
<td>Methylphenidate, 54 mg/d</td>
<td>Risperidone, 2 mg/d, methylphenidate, 36 mg/d</td>
</tr>
<tr>
<td>None stated</td>
<td>2 mg/d</td>
<td>Duloxetine, 80 mg/d, clonazepam, 2 mg/d</td>
<td>Duloxetine, 120 mg/d</td>
</tr>
<tr>
<td>Abrupt decrease of amisulpride dose from 800 mg/d to 400 mg/d</td>
<td>20 mg/d</td>
<td>Biperiden, 4 mg/d</td>
<td>Amisulpride, 800 mg/d</td>
</tr>
<tr>
<td>Haloperidol, 20 mg/d, abrupt clozapine discontinuation</td>
<td>15 mg/d</td>
<td>Valproic acid, nortriptyline</td>
<td>Molindone, 150 mg/d</td>
</tr>
<tr>
<td>Tapered amisulpride, 400 mg/d, over 6 weeks</td>
<td>15 mg/d</td>
<td>None</td>
<td>Amisulpride, 600 mg/d</td>
</tr>
<tr>
<td>Discontinued ziprasidone, 200 mg/d</td>
<td>30 mg/d</td>
<td>Lorazepam, 2 mg/d, amantadine, 100 mg, sertraline, 50 mg/d</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Decreased quetiapine dose from 800 mg/d to 400 mg/d</td>
<td>15 mg/d</td>
<td>Divalproex, 1,000 mg/d, fluvoxamine, 200 mg/d, clonazepam, 2 mg/d</td>
<td>Lithium, quetiapine, 500 mg/d, haloperidol, 2 mg/d</td>
</tr>
<tr>
<td>Risperidone, 3 mg/d, interruption of fluphenazine, 75 mg/d</td>
<td>20 mg/d</td>
<td>Divalproex, 4,500 mg/d, benztrpine, 3 mg/d</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Discontinued amisulpride, 800 mg/d over 2 weeks</td>
<td>30 mg/d</td>
<td>Lithium</td>
<td>Amisulpride, 500 mg/d</td>
</tr>
<tr>
<td>Discontinued risperidone, 2 mg/d, over 2 weeks</td>
<td>15 mg/d</td>
<td>Lithium</td>
<td>Risperidone, 4 mg</td>
</tr>
<tr>
<td>Reduced risperidone dosage from 5 mg/d to 4 mg/d</td>
<td>7.5 mg/d</td>
<td>None</td>
<td>Risperidone, 5 mg/d</td>
</tr>
<tr>
<td>None</td>
<td>60 mg/d</td>
<td>None</td>
<td>Aripiprazole dose reduction to 15 mg/d, olanzapine, 10 mg/d</td>
</tr>
<tr>
<td>Tapered and discontinued thioridazine, 600 mg/d, over 3 months</td>
<td>30 mg/d</td>
<td>None</td>
<td>Chlorpromazine, 200 mg/d, aripiprazole, 30 mg/d</td>
</tr>
<tr>
<td>Decreased olanzapine dose from 30 mg/d to 20 mg/d</td>
<td>30 mg/d</td>
<td>None</td>
<td>Olanzapine, 30 mg/d</td>
</tr>
<tr>
<td>Discontinued perphenazine, 8 mg/d</td>
<td>30 mg/d</td>
<td>None</td>
<td>Quetiapine, 350 mg/d</td>
</tr>
<tr>
<td>Haloperidol, 200 mg/d</td>
<td>15 mg/d</td>
<td>Benztrpine</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Olanzapine, 60 mg/d</td>
<td>10 mg/d</td>
<td>None</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Discontinued ziprasidone, 160 mg/d, discontinued quetiapine, 400 mg/d, over 2 weeks</td>
<td>30 mg/d</td>
<td>Propranolol, 30 mg/d, l-thyroxine, .05 mg/d, carbamazepine, 600 mg/d</td>
<td>Not available</td>
</tr>
<tr>
<td>Decreased olanzapine dose from 20 mg/d to 15 mg/d</td>
<td>30 mg/d</td>
<td>Valproic acid, 2,000 mg/d</td>
<td>Ziprasidone</td>
</tr>
<tr>
<td>Decreased ziprasidone dose from 200 mg/d to 160 mg/d 2 months previously</td>
<td>30 mg/d</td>
<td>Carbamazepine, 200 mg/d</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Risperidone, 3 mg/d</td>
<td>15 mg/d</td>
<td>Valproic acid, 1,500 mg/d</td>
<td>Risperidone, 3 mg/d</td>
</tr>
<tr>
<td>Quetiapine, 800 mg/d</td>
<td>30 mg/d</td>
<td>Divalproex, 2,000 mg/d</td>
<td>Olanzapine, 20 mg/d</td>
</tr>
</tbody>
</table>

**Clinical Point**
Covert akathisia may not explain worsening psychopathology observed in all patients in our literature review.
Related Resource


Drug Brand Names

- Amanadine • Symmetrel
- Aripiprazole • Abilify
- Benzotropine •Cogentin
- Biperiden • Akineton
- Carbamazine • Tegetrol
- Chlorpromazine • Thorazine
- Clonazepam • Klonopin
- Clozapine • Clozaril
- Divalproex • Depakote
- Duloxetine • Cymbalta
- Fluoxetine • Prozac
- Haloperidol • Haldol
- Lithium • Eskalith, Lithobid
- Lorazepam • Ativan
- Nortriptiline • Aventyl,
- Perphenazine • Trilafon
- Propranolol • Inderal
- Valproic acid • Depakene
- Thyroxine • Synthroid
- Prolixin
- Depakote
- Sertraline • Zoloft
- Thioridazine • Mellaril
- Thymoxine • Synthroid
- Valproic acid • Depakene
- Ziprasidone • Geodon

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

all patients in our literature review because confusion of akathisia and worsening psychosis is not a widespread phenomenon. In a post hoc analysis of pooled safety data from aripiprazole trials, Kane et al31 did not find a correlation between presence of akathisia and aripiprazole efficacy as measured by the Positive and Negative Symptom Scale (PANSS) total, PANSS positive, PANSS negative, Clinical Global Impressions-Severity, Clinical Global Impressions-Improvement, and percentage of responders. Pae et al25 also noted there was no correlation between scores on the Barnes Akathisia Rating Scale and worsening psychopathology in patients switched to aripiprazole.

An antagonist always is an antagonist and clinicians have appreciated this concept since the days of chlorpromazine. The activity of aripiprazole, however, is on a pharmacologic continuum between a neutral antagonist and full agonist and currently there is no way to precisely determine the level of D2 receptor agonist action in a patient.

Although it is interesting to speculate that aripiprazole’s D2 receptor agonist action may contribute to worsening psychosis,23-24 there are other plausible explanations to consider. Rapid transition from a drug with significant anticholinergic properties and aripiprazole-associated akathisia may contribute to worsening psychopathology in patients starting aripiprazole. Because covert side effects may be incorrectly identified as psychotic agitation, we cannot exclude this as a possible etiologic factor in Mr. N’s case as well as the cases in our literature review.

References

18. Masri B, Salahpour A, Didrikson M, et al. Antagonism of dopamine D2 receptor/beta-arrestin 2 interaction is a common property of clinically effective antipsychotics. Proc...


References