Antipsychotics for nonpsychotic illness

Limited evidence suggests possible efficacy based on known receptor binding affinities

Second-generation antipsychotics (SGAs) represent 5% of all U.S. drug expenditures. Their use for indications not approved by the FDA (“off-label” use) increased to a total of $6 billion in 2008, $5.4 billion of which was for uses with limited or uncertain evidence.

Off-label use of antipsychotics usually is based on novel applications of known receptor binding affinities (Table 1, page 24). For example, antipsychotics with strong antihistamine effects may promote sedation and could be used to treat insomnia. Clinicians also might use antipsychotics to treat a specific symptom of an illness when other treatment options are limited or when patients do not respond to standard treatments.

To safely use any medication off-label, clinicians should become familiar with literature on the proposed use. Clinicians should consider off-label use only after carefully weighing the potential therapeutic benefits against the risks. Patients should be aware that the prescribed use is not FDA-approved and informed consent should include a discussion of alternative treatments. The high cost of SGAs may be a limiting factor and should be discussed with patients.

This article reviews the evidence for using antipsychotics to treat insomnia, tics, delirium, and stuttering (Table 2, page 25). See this article at CurrentPsychiatry.com for a review of the evidence supporting antipsychotics for treating migraine and cluster headaches and nausea.

**Current use of antipsychotics**

Antipsychotics are divided into 2 major classes—first-generation antipsychotics (FGAs) and SGAs—and principally are FDA-approved for
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Treating schizophrenia. Some antipsychotics have received FDA approval for maintenance treatment of schizophrenia and bipolar disorder (BD), and others have been approved to treat tic disorders (haloperidol and pimozide).

To varying degrees, all antipsychotics block D2 receptors, which is thought to be necessary for treating psychosis. However, some SGAs have significant affinity at other receptors—such as 5-HT2A and 5-HT1A—that confer additional properties that are not fully understood. For example, it is believed that 5-HT2A blockade in the striatum reduces the potential for extrapyramidal symptoms (EPS).

Each antipsychotic blocks a unique set of receptors in the brain, leading to a specific set of intended and potentially unintended effects. For example, olanzapine’s effect on psychosis largely stems from its action at the D2 receptor, whereas its sedative and anticholinergic properties are a result of activity at histamine (H1) receptors and muscarinic receptors, respectively. Clinicians can make rational use of unintended effects by carefully selecting a medication based on receptor binding profile (eg, using an antipsychotic with sedating properties in a patient who has psychosis and insomnia). This approach can limit use of multiple medications and maximize a medication’s known effects while attempting to minimize side effects.

Insomnia

Clinicians use FGAs and SGAs to treat insomnia because of their sedating effects, although evidence supporting this use is questionable. Among the FGAs, chlorpromazine produces moderate to severe sedation, whereas haloperidol is only mildly sedating. Clozapine is believed to be the most sedating SGA, whereas quetiapine and olanzapine produce moderate sedation.

Most data on antipsychotics’ sedating effects comes from studies completed for schizophrenia or BD. Few studies have evaluated using antipsychotics to treat primary insomnia or other sleep disorders in otherwise healthy patients. However, data from phase I studies of antipsychotics has shown that schizophrenia patients tolerate a higher maximum dose compared with healthy volunteers, who often experience more sedation.

An antipsychotic’s potential for sedation is directly related to its affinity at H1 receptors and total drug concentration at the H1 receptor binding site. Because drugs with lower affinity for D2 receptors typically are prescribed at higher doses when treating psychiatric illness, the corresponding concentration at H1 receptors can lead to greater sedation compared with equivalent doses of higher-potency agents.

The same phenomenon is seen with high-potency agents. Haloperidol has a
relatively weak binding affinity to the H1 receptor, but causes more sedation at higher doses. Haloperidol, 20 mg/d, produces sedation in more patients than a moderate dose of risperidone, 2 to 10 mg/d. These observations correlate with “the high milligram-low-potency” spectrum seen with FGAs.

Among SGAs, a double-blind, placebo-controlled, crossover study of the effects of ziprasidone, 40 mg/d, on sleep in a group of healthy volunteers found a significant increase in total sleep time and sleep efficiency. A double-blind trial compared patients taking low, medium, or high daily doses of olanzapine with patients receiving haloperidol or placebo. Sedation was reported in 20% of patients taking low doses of olanzapine (5 ± 2.5 mg/d) compared with 29.7% on medium doses (10 ± 2.5 mg/d) and 39.1% on high doses (15 ± 2.5 mg/d).

A double-blind, placebo-controlled, crossover study demonstrated that olanzapine produced significant increases in sleep continuity, slow wave sleep, and subjective ratings of sleep quality in healthy men. Similarly, a study comparing haloperidol, 12 mg/d, and quetiapine, 75 to 750 mg/d, for treating acute schizophrenia found an 8% to 11% incidence of somnolence in the quetiapine group compared with 6% and 8% in the haloperidol and placebo groups, respectively. Somnolence was reported as an adverse event in these studies, which were designed to examine the drug’s effect on acute schizophrenia and did not evaluate its effect on sleep.

A double-blind, placebo-controlled, crossover study examining quetiapine’s effects on sleep in 14 healthy patients demonstrated a significant difference in total sleep time, sleep period time, and sleep efficiency. Similarly, an open-label pilot study of quetiapine’s effect on primary insomnia showed significant improvement in total sleep time and sleep efficiency.

Studies examining quetiapine’s effects on insomnia in patients with substance abuse and women with localized breast cancer showed improved sleep scores on multiple assessment tools, while an open-label study of quetiapine for Parkinson’s disease demonstrated decreased sleep latency. Adjunctive quetiapine administered over a 6-week, open-label trial in veterans with posttraumatic stress disorder revealed significant improvement from

### Table 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Strength of evidence*</th>
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<tbody>
<tr>
<td>Insomnia</td>
<td>Weak to intermediate: Haloperidol, olanzapine, quetiapine, risperidone, ziprasidone</td>
</tr>
</tbody>
</table>
| Tics of Tourette’s disorder | Strong: Haloperidol, pimozide  
Intermediate: Chlorpromazine, fluphenazine, penfluridol, perphenazine, thioridazine, trifluoperazine  
Weak: Risperidone  
Very weak: Aripiprazole, olanzapine, quetiapine, ziprasidone |
| Delirium                  | Intermediate: Haloperidol  
Weak: Olanzapine, quetiapine, risperidone  
Very weak: Aripiprazole, ziprasidone |
| Stuttering                | Very weak: Chlorpromazine, haloperidol, olanzapine, risperidone |

*Strong: Multiple, well-designed RCTs directly relevant to the recommendation, yielding consistent findings  
Intermediate: Some evidence from RCTs that support the recommendation, but the scientific support was not optimal  
Weak: Consensus recommendation in the absence of relevant RCTs and better evidence than case report or series  
Very weak: Case reports, case series, or preliminary studies  
RCTs: randomized controlled trials

**Source:** For a bibliography of the studies considered, see this article at CurrentPsychiatry.com

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**Clinical Point**

Clozapine is believed to be the most sedating SGA, whereas quetiapine and olanzapine produce moderate sedation.
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Sedating antipsychotics such as thioridazine and chlorpromazine historically were used off-label for insomnia, but fell out of favor because of their associated cardiac risks. More recently, clinicians have been using SGAs in a similar manner even though SGAs are costly and have significant risks such as metabolic problems. Studies supporting the use of SGAs for the short-term or long-term treatment of insomnia are limited by small sample sizes or open-label designs. In 2005 the National Institutes of Health State-of-the-Science Conference Panel did not recommend using SGAs for treating chronic insomnia.

Tics in Tourette’s disorder
FGAs and SGAs have been used to treat tics associated with Tourette’s disorder (TD). Haloperidol is FDA-approved for treating tics in adult and pediatric patients.

Clinical Point
In veterans with PTSD, adjunctive quetiapine improved sleep quality and duration and diminished dreaming.

Table 3

# Antipsychotics: Receptor pharmacology and common side effects

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Pharmacology</th>
<th>Common side effects&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prochlorperazine&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>D2 receptor antagonist and α-1 adrenergic receptor antagonism</td>
<td>EPS, akathisia, prolactinemia, orthostatic hypotension, altered cardiac conduction, agranulocytosis, sexual dysfunction</td>
</tr>
<tr>
<td>Chlorpromazine&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>D2 receptor antagonist. Also binds to H1 and cholinergic M1</td>
<td>EPS, akathisia, prolactinemia, orthostatic hypotension, urinary retention, non-specific QT changes, agranulocytosis, sexual dysfunction</td>
</tr>
<tr>
<td>Droperidol&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>D2 receptor antagonist and antagonist at peripheral α-1 activity</td>
<td>EPS, akathisia, prolactinemia, QT changes (dose dependent)</td>
</tr>
<tr>
<td>Haloperidol&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>D2 receptor antagonist. Also binds to D1, 5-HT2, H1, and α-2 adrenergic receptors</td>
<td>EPS, akathisia, prolactinemia, QT changes (dose dependent)</td>
</tr>
<tr>
<td>Aripiprazole&lt;sup&gt;a,c,d&lt;/sup&gt;</td>
<td>D2 and 5-HT1A partial agonism, 5-HT2A antagonism</td>
<td>Akathisia, EPS, sedation, restlessness, insomnia, tremor, anxiety, nausea, vomiting, possible weight gain (20% to 30%)</td>
</tr>
<tr>
<td>Clozapine&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>5-HT2, D1, D2, D3, D4, M1, H1, α-1, and α-2 antagonism</td>
<td>Sedation, dizziness, tachycardia, weight gain, nausea, vomiting, constipation</td>
</tr>
<tr>
<td>Olanzapine&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>5-HT2A, 5-HT2C, D1, D2, D3, D4, M1-5, H1, and α1-antagonism</td>
<td>Sedation, EPS, prolactinemia, weight gain, constipation</td>
</tr>
<tr>
<td>Quetiapine&lt;sup&gt;a,c,d&lt;/sup&gt;</td>
<td>D1, D2, 5-HT2A, 5-HT1A, H1, α-1, and α-2 antagonism</td>
<td>Sedation, orthostatic hypotension, weight gain, triglyceride abnormalities, hypertension (frequently diastolic), constipation</td>
</tr>
<tr>
<td>Risperidone&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>5-HT2, D2, H1, α-1, and α-2 antagonism</td>
<td>Sedation, akathisia, EPS, prolactinemia, weight gain, tremor</td>
</tr>
<tr>
<td>Ziprasidone&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>D2, D3, 5-HT2A, 5-HT2C, 5-HT1D, and α-1 antagonism; moderate inhibition of 5-HT and NE reuptake; 5-HT1A agonism</td>
<td>EPS, sedation, headache, dizziness, nausea</td>
</tr>
</tbody>
</table>

<sup>a</sup>Side effects and their prominence usually are based on receptor binding profile. All antipsychotics to varying degrees share the following symptoms: EPS, neuroleptic malignant syndrome, QTc prolongation, anticholinergic side effects (urinary retention, decreased gastrointestinal motility, xerostomia), sedation, orthostatic hypotension, blood dyscrasias, and problems with temperature regulation. The class as a whole also carries a “black-box” warning regarding increased mortality when treating geriatric patients with psychosis related to dementia.

<sup>b</sup>No frequencies were available

<sup>c</sup>Only side effects with frequency >10% listed

<sup>d</sup>“Black-box” warning for suicidal ideation and behavior in children, adolescents, and young adults (age 18 to 24) with major depressive disorder and other psychiatric disorders

<sup>e</sup>“Black-box” warnings for agranulocytosis, myocarditis, orthostatic hypotension, seizure risk

EPS: extrapyramidal symptoms; H1: histamine; M1: muscarinic; NE: norepinephrine

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with TD. Many studies have reported the efficacy of haloperidol in this population; however, cognitive blunting, weight gain, lethargy, and akathisia limit its use.  

Pimozide, the most widely used alternative to haloperidol for treating TD, can cause clinically significant QTc prolongation and sudden death. Penfluridol demonstrated significant symptomatic improvement compared with haloperidol in 1 study, but its carcinogenic potential limits its use.  

A double-blind, placebo-controlled study comparing fluphenazine and trifluoperazine with haloperidol for treating TD showed that both are significantly more effective than placebo, but none was more effective than the others.  

Studies show chlorpromazine, perphenazine, and thioridazine are less effective than haloperidol and their use is limited by photosensitivity, dermatitis, EPS, and blood and liver dyscrasias.  

Risperidone is superior to placebo for treating tics associated with TD. A placebo-controlled trial of ziprasidone showed the drug has efficacy similar to risperidone in reducing tics in children and adolescents with TD. However, ziprasidone is not FDA-approved for this use.  

Evidence supporting the use of other SGAs for treating TD is more limited. Several small studies of olanzapine and aripiprazole had limited but favorable results. Quetiapine has not been studied for treating TD, but several case reports have indicated a positive response. In a double-blind, placebo-controlled trial, clozapine showed no therapeutic benefit for TD.  

Although not FDA-approved, it is recommended by the Society of Critical Care Medicine as a safe, cost-effective, and efficacious therapy for the psychiatric symptoms associated with delirium.  

The most extensively studied SGA for treating delirium, risperidone often is used as an alternative to haloperidol. Case reports describe its potential efficacy. In a head-to-head study, risperidone was as effective as low-dose haloperidol for acute delirium treatment.  

Olanzapine was effective in managing delirium in several case studies. Also, in a 7-day, randomized, placebo-controlled study, olanzapine and haloperidol showed significantly greater and relatively equivalent improvement compared with placebo; patients treated with olanzapine experienced more rapid improvement in 1 study.  

Case reports and prospective studies also have described quetiapine as effective for treating delirium. In a prospective, double-blind, placebo-controlled study, patients taking quetiapine had a faster resolution of delirium with reduced overall duration and less agitation than those taking placebo. Mortality, intensive care unit length of stay, and incidence of QTc prolongation did not differ, but patients treated with quetiapine were more likely to have increased somnolence and were more frequently discharged to home or rehabilitation centers. One limitation of the study is that concomitant haloperidol use on an “as needed” basis was permitted.  

Evidence supporting the efficacy of ziprasidone for delirium is limited to case reports. In 1 case report, a patient with chronic HIV infection and acute cryptococcal meningitis experienced significant improvement of delirium symptoms but could not continue ziprasidone because of fluctuating QTc intervals.  

In 2 patients with delirium, aripiprazole, 15 and 30 mg/d, improved confusion, disorientation, and agitation within 7 days. In another study of delirium, 13 of 14 patients on flexibly dosed aripiprazole (5 to 15 mg/d) showed improvement in Clinical Global Impressions Scale scores, although 3 patients developed prolonged QTc intervals.  

**Clinical Point**

Haloperidol is FDA-approved for treating tics; however, cognitive blunting, weight gain, lethargy, and akathisia limit its use.
Stuttering or stammering

Stuttering or stammering are age-appropriate disturbances in normal fluency and time patterning of speech. The evidence for antipsychotics to treat stuttering or stammering speech mainly consists of case reports and does not include disfluency frequency data, which makes it difficult to accept claims of efficacy. Disfluency frequency data describe how often a patient has specific disfluencies (blocks, prolongations, interjection, and repetition of syllables, words, or phrases).

Two FGAs (chlorpromazine and haloperidol) and 2 SGAs (risperidone and olanzapine) have been evaluated for treatment. Children were 2.5 times more likely to demonstrate significant improvement when taking chlorpromazine vs placebo. An open-label study of haloperidol lacked disfluency frequency data, therefore casting doubts on haloperidol’s reported efficacy in the study.

In a case report, a 4-year-old boy with severe behavioral dyscontrol showed complete remission of stammering after 1 day of risperidone, 0.25 mg/d. The patient’s symptoms reappeared several days after the drug was stopped. In a case series of 2 patients with developmental stuttering, 1 patient reported significant improvement in fluency with olanzapine, 2.5 mg/d, and the other showed marked improvement in fluency with 5 mg/d.46

References
Bottom Line

Although evidence supporting most uses of antipsychotics for nonpsychotic illness is lacking, clinicians can rationally use specific drugs to treat certain symptoms based on application of known receptor binding affinities when they lack alternatives or when standard treatments are ineffective or intolerable. Off-label antipsychotic use carries risks; carefully weigh these decisions with patients. Clinicians should be familiar with the literature before using a medication for a non-approved indication.

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Clinical Point

Children were 2.5 times more likely to show improvement in stuttering when taking chlorpromazine vs placebo.
Antipsychotics for nonpsychotic illness: What does the evidence say?

INSOMNIA


TICS OF TOURETTE’S DISORDER


DELIRIUM


STUTTERING


