Antipsychotics for nonpsychotic illness

Limited evidence suggests possible efficacy based on known receptor binding affinities

Aveekshit Tripathi, MD
Senior Resident
Psychiatry and Behavioral Sciences

Matthew Macaluso, DO
Assistant Professor, Psychiatry and Behavioral Sciences
Associate Director, Residency Training

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University of Kansas School of Medicine-Wichita
Wichita, KS

Second-generation antipsychotics (SGAs) represent 5% of all U.S. drug expenditures.[1] 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.[1]

Off-label use of antipsychotics usually is based on novel applications of known receptor binding affinities (*Table 1, page 24*).[2-5] 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[6] 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

Table 1

Possible rationales for antipsychotic use for nonpsychotic conditions

Condition	Possible rationale
Insomnia[2]	Effects on H1, α-1 adrenergic, and muscarinic cholinergic receptors. 5-HT2 antagonism activity also has been implicated
Tics of Tourette's disorder[3]	By blocking dopamine receptors, antipsychotics decrease the primarily dopaminergic input from the substantia nigra and ventral tegmentum to the basal ganglia
Delirium[4]	Patients have reversible impairment of cerebral oxidative metabolism and multiple neurotransmitter abnormalities (dopamine, acetylcholine, CNS γ-aminobutyric acid, and serotonin). Other hypotheses include inflammatory reactions, damage to certain structural pathways, and disruption of cortisol and β-endorphin circadian rhythms
Stuttering[5]	Stutterers have a marked increase in dopaminergic afferent activity in the tail of the left caudate nucleus compared with healthy controls

H1: histamine

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 (*Table 3, page 26*). 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 untoward 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.[7]

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.[2] 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

Antipsychotics for nonpsychotic disorders: Strength of the evidence

Condition	Strength of evidence[a]
Insomnia	Weak to intermediate: Haloperidol, olanzapine, quetiapine, risperidone, ziprasidone
Tics of Tourette's disorder	Strong: Haloperidol, pimozide
	Intermediate: Chlorpromazine, fluphenazine, penfluridol, perphenazine, thioridazine, trifluoperazine
	Weak: Risperidone
	Very weak: Aripiprazole, olanzapine, quetiapine, ziprasidone
	Not effective: Clozapine
Delirium	Intermediate: Haloperidol
	Weak: Olanzapine, quetiapine, risperidone
	Very weak: Aripiprazole, ziprasidone
Stuttering	Very weak: Chlorpromazine, haloperidol, olanzapine, risperidone

[a]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

Clinical Point

Clozapine is believed to be the most sedating SGA, whereas quetiapine and olanzapine produce moderate sedation

relatively weak binding affinity to the H1 receptor,[8] 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.[8] These observations correlate with "the high milligram-low-potency" spectrum seen with FGAs.[7]

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.[9] A double-blind trial compared patients taking low, medium, or high daily doses of olanzapine with patients receiving haloperidol or placebo.[10] 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).[10]

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.[11] 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.[12] 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.[13] Similarly, an open-label pilot study of quetiapine's effect on primary insomnia showed significant improvement in total sleep time and sleep efficiency.[14]

Studies examining quetiapine's effects on insomnia in patients with substance abuse[15] and women with localized breast cancer[16] showed improved sleep scores on multiple assessment tools, while an open-label study of quetiapine for Parkinson's disease demonstrated decreased sleep latency.[17] Adjunctive quetiapine administered over a 6-week, open-label trial in veterans with posttraumatic stress disorder revealed significant improvement from

Table 3

Antipsychotics: Receptor pharmacology and common side effects

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

[a]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
[b]No frequencies were available
[c]Only side effects with frequency >10% listed
[d]"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
[e]"Black-box" warnings for agranulocytosis, myocarditis, orthostatic hypotension, seizure risk

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

baseline in sleep quality and duration and diminished dreaming.[18]

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[19] 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.[20] In 2005 the National Institutes of Health State-of-the-Science Conference Panel did not recommend using SGAs for treating chronic insomnia.[21]

Tics in Tourette's disorder

FGAs and SGAs have been used to treat tics associated with Tourette's disorder (TD).[22] Haloperidol is FDA-approved for treating tics in adult and pediatric patients

with TD. Many studies have reported the efficacy of haloperidol in this population; however, cognitive blunting, weight gain, lethargy, and akathisia limit its use.[23]

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.[24]

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.[25] 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.[26]

Risperidone is superior to placebo for treating tics associated with TD.[27] A placebo-controlled trial of ziprasidone showed the drug has efficacy similar to risperidone in reducing tics in children and adolescents with TD.[28] 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.[29]

Delirium

American Psychiatric Association practice guidelines suggest using psychotropic medications to treat neuropsychiatric symptoms of delirium.[30] Antipsychotics are considered first-line agents that lower hospital mortality rates, decrease lengths of hospital stays, and improve delirium symptoms, in some cases before the underlying medical etiologies resolve.[30,31] Available in liquid, oral, IM, and IV formulations, haloperidol is the mainstay of symptomatic treatment of delirium.[31]

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.[32] In a head-to-head study, risperidone was as effective as low-dose haloperidol for acute delirium treatment.[33]

Olanzapine was effective in managing delirium in several case studies.[34] 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.[35]

Case reports and prospective studies also have described quetiapine as effective for treating delirium.[36,37] 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.[37] 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.[38]

Evidence supporting the efficacy of ziprasidone for delirium is limited to case reports.[39] 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.[40]

In 2 patients with delirium, aripiprazole, 15 and 30 mg/d, improved confusion, disorientation, and agitation within 7 days.[41] 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.[42]

Clinical Point

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

Related Resources

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Drug Brand Names

Aripiprazole • Abilify	Pimozide • Orap
Chlorpromazine • Thorazine	Prochlorperazine • Compazine
Clozapine • Clozaril	
Fluphenazine • Permitil, Prolixin	Quetiapine • Seroquel
	Risperidone • Risperdal
Haloperidol • Haldol	Thioridazine • Mellaril
Olanzapine • Zyprexa	Trifluoperazine • Stelazine
Perphenazine • Trilafon	Ziprasidone • Geodon

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Stuttering or stammering

Stuttering or stammering are age-inappropriate 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 treating stuttering. Children were 2.5 times more likely to demonstrate significant improvement when taking chlorpromazine vs placebo.[43] An open-label study of haloperidol lacked disfluency frequency data, therefore casting doubts on haloperidol's reported efficacy in the study.[44]

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.[45] 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]

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Clinical Point

Children were 2.5 times more likely to show improvement in stuttering when taking chlorpromazine vs placebo

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.

Current PSYCHIATRY

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Antipsychotics for nonpsychotic illness: What does the evidence say?

INSOMNIA

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