Current PSYCHIATRY

Why off-label antipsychotics remain first-choice drugs for delirium

Short-term, low-dose therapy appears to be worth the risk, despite black-box warning

Delirium is a medical emergency that needs to be identified and treated vigorously. Antipsychotics—including haloperidol and atypical agents—effectively manage a wide spectrum of delirium symptoms and are an essential component in the standard multimodal approach.[1] Even so, antipsychotics are not FDA-approved for treating delirium, and evidence on their safety in medically ill patients is limited—particularly in the elderly, in whom delirium occurs most often.

The FDA has warned of increased risk of death when atypical antipsychotics are used to treat behavioral disturbances in elderly patients with dementia.[2] Similarly, a retrospective study of elderly patients taking antipsychotics found higher mortality rates associated with typical antipsychotics than with atypicals.[3]

This article discusses the risks and benefits of using antipsychotics to manage delirium. Based on the literature and clinical experience, we offer recommendations on choosing among the available agents and avoiding side effects.

A challenging diagnosis

Delirium is a neuropsychiatric syndrome precipitated by an underlying medical condition or a medication effect on the brain. Its characteristic symptoms—abrupt onset of disturbed consciousness, attention, cognition, and perception—tend to fluctuate during the day. Delirium most often occurs in elderly patients ***(Box, page 50)***[1,4-7]—particularly with dementia—but also occurs

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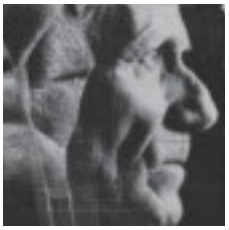


Delirium

Clinical Point

Comparison trials have not identified any antipsychotic as more efficacious than another in treating delirium

Box

Delirium: Harbinger of death in the elderly

Up to 1 in 4 patients (14% to 24%) have delirium at hospital admission, and the annual incidence of delirium is 6% to 56% among hospital populations.[4] Elderly inpatients who develop delirium have an estimated mortality rate of 22% to 76% during that hospitalization.[1] At the end of life, the prevalence of delirium may be as high as 85%.[5]

Serotonergic, noradrenergic, opiatergic, glutamatergic, and histaminergic neurotransmitter systems may contribute to delirium as a syndrome. Evidence implicates underactivity of the cholinergic system as the final common pathway.[6,7]

The acetylcholine-dopamine hypothesis explains the efficacy of dopamine antagonists in treating delirium by regulating the imbalance between cholinergic and dopaminergic activity.[5,6] Cytokines—including interleukin-1, interleukin-2, and interleukin-6—and chronic hypercortisolism may also contribute to delirium.[4]

in younger patients with serious illnesses such as cancer or HIV-AIDS.

Delirium is underdiagnosed and undertreated in medical settings,[4,8] most likely because of its protean symptoms (***Table 1***)[9] and fluctuating clinical findings. Neurologic abnormalities—including cortical and motor symptoms—also can occur.[1]

Mortality risk. Delirium is an independent risk factor for mortality.[1,4,5] It is a marker for serious and potentially life-threatening medical problems, such as organ failure or sepsis. When antipsychotics fail to control delirium, the 3 most common reasons are:

- delirium's etiology has not been discovered or addressed
- delirium's etiology is resistant to treatment or potentially irreversible
- antipsychotic dosage was inadequate.

Given the first 2 reasons, patients with uncontrolled delirium are likely to be more seriously ill and less likely to recover than those whose delirium more readily resolves. After prolonged episodes, patients also may have decreased cognitive function post-delirium.

3 subtypes. Delirium is classified as hyperactive, hypoactive, or mixed, depending on arousal disturbance and psychomotor behavior:

- the hyperactive subtype includes hallucinations, delusions, agitation, and disorientation.
- the hypoactive subtype includes confusion, sedation, and decreased alertness but rarely hallucinations or delusions.[1]

In two-thirds of delirium cases, patients show hypoactive or mixed symptoms.

Antipsychotics: Limited evidence

The multimodal approach for managing delirium includes:

- identifying and eliminating contributing factors
- instituting nonpharmacologic interventions based on environmental strategies (***Table 2***)[4]
- providing pharmacologic interventions—primarily antipsychotics—as needed.

Clinical trials. Most studies of antipsychotics for delirium have been open-label trials, case reports, and retrospective reviews. A review of 14 prospective studies[10] showed that:

- delirium severity improved with haloperidol, chlorpromazine, olanzapine, risperidone, or quetiapine
- comparison trials did not identify any antipsychotic as more efficacious than another.

Serious adverse events attributable to antipsychotics were uncommon, although most trials did not systematically evaluate side effects. None included a placebo comparison to explain spontaneous improvements in delirium. The authors concluded that evidence is limited for using low-dose antipsychotics for short-term delirium treatment.

Michaud et al[11] reviewed guidelines, systematic reviews, randomized controlled trials, and cohort studies on delirium man-

agement. They concluded that the experts agree on 3 points:

- prevention should be emphasized
- atypical antipsychotics are not first-choice drugs because of data on adverse events in the elderly
- pharmacologic treatment is recommended when the patient's condition prevents adequate care or puts the patient or staff at risk.

Conclusion. We believe these findings signify the lack of sufficient data on pharmacologic treatment of delirium. Further research is needed to assess the efficacy of antipsychotics in delirium treatment.

Conventional antipsychotics

Haloperidol, the most-studied antipsychotic in delirium treatment, often is the drug of choice because of its high potency, low sedative effect, few anticholinergic side effects, minimal cardiovascular side effects, no active metabolites, and multiple administration routes.[1]

An IV route can facilitate rapid onset of medication effects. Compared with oral haloperidol, IV administration is associated with a lower risk of extrapyramidal symptoms (EPS), which allows use of higher doses.

Any IV use of injectable haloperidol is off-label, however. If you choose the IV route, monitor patients carefully for cardiac arrhythmias. Haloperidol's prescribing information carries a new warning of sudden death, QT prolongation, and torsades de pointes in patients given IV haloperidol.

Chlorpromazine. In a double-blind, randomized comparison trial of 30 hospitalized AIDS patients, our group[12] found oral and IM haloperidol (n=11) or chlorpromazine (n=13) highly effective in controlling delirium. Delirium symptoms improved significantly in both hypoactive and hyperactive subtypes with low doses of either antipsychotic (approximately 2 mg of haloperidol equivalent/day).

No patients developed dystonic or dyskinetic symptoms. Lorazepam, given to 6 patients, worsened delirium and cognitive impairment.

Table 1

Recognizing delirium: Diagnostic clinical features*

Altered level of alertness and arousal
Rapidly fluctuating course
Attention disturbance
Increased or decreased psychomotor activity
Disturbance of sleep-wake cycle
Affective symptoms
Altered perceptions
Disorganized thinking and incoherent speech
Disorientation and memory impairment

* Not all symptoms are present in every case.
Source: Reference 9

Table 2

Nonpharmacologic approaches to managing delirium

Search for and correct all causes of delirium, including underlying disease or a medication effect
Create a calm, comfortable environment
Provide orienting objects such as calendars and clocks
Have family members present
Limit room and staff changes
Allow patients uninterrupted rest at night to improve the sleep-wake cycle
Consider 1-to-1 nursing observation, as necessary

Source: Reference 4

Atypicals in delirium: Trial data

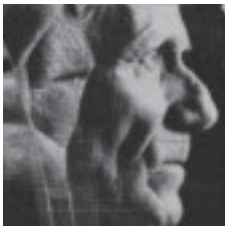
Risperidone. Three open-label studies of risperidone in patients with delirium reported minimal risk of sedation and EPS.[13-15]

A 7-day, double-blind, flexible-dose trial of 24 patients with delirium[16] found no significant difference between haloperidol (mean 1.71 mg/d) and risperidone (mean 1.02 mg/d) in clinical efficacy or response rate. The authors acknowledged, that they were unable to obtain identical-looking haloperidol and risperidone tablets for the trial.

Kim et al[17] studied dopamine trans-

Clinical Point

Haloperidol is often the drug of choice for delirium because of its high potency, low sedative effect, and few anticholinergic side effects



Delirium

Clinical Point

Consider the patient's risk of EPS, sedation, anticholinergic side effects, cardiac arrhythmias, and drug interactions

porter gene polymorphism and use of haloperidol vs risperidone in 42 patients with delirium. Relatively low doses of both antipsychotics showed similar efficacy, and the authors concluded that dopamine transporter gene polymorphism did not influence delirium treatment.

Olanzapine. In an open trial of 79 inpatients with advanced cancer, olanzapine (mean 6.3 mg/d, range 2.5 to 20 mg/d) resolved delirium in 76% of patients, with no incidence of EPS.[18] Age >70, history of dementia, hypoxia, cerebral metastasis, and hypoactive delirium were associated with poor response to olanzapine. This study is unique in assessing olanzapine's efficacy in different delirium subtypes.

A prospective, randomized trial compared olanzapine (mean 4.5 mg/d, range 2.5 to 13.5 mg/d) with haloperidol (mean 6.5 mg/d, range 1 to 28 mg/d) in patients admitted with delirium to a critical care setting.[19] Both treatment groups showed similar improvement over 5 days. No side effects were reported in the patients receiving olanzapine.

Quetiapine. A few authors have published their experience with quetiapine in treating delirium. An open-label, flexible-dose trial of 22 inpatients[20] showed significant improvement in delirium severity with the use of quetiapine. No patients experienced EPS; sedation was the most common side effect.

Ziprasidone. In the first case report in which ziprasidone was used to treat delirium,[21] an HIV/AIDS patient was given 100 mg/d. Delirium symptoms improved, but treatment was discontinued because of side effects (hypokalemia, hypomagnesemia, premature ventricular contractions, and QT interval prolongation).

Aripiprazole. Straker et al[22] reported 14 cases delirium treated with aripiprazole, which showed few side effects. Twelve patients had a ≥50% decrease in Delirium Rating Scale scores, and 13 showed improvement in Clinical Global Impression scale scores.

Clinical options

When choosing an antipsychotic to treat delirium, consider the individual patient's risks of EPS, sedation, anticholinergic side effects, cardiac arrhythmias, and drug-drug interactions.

Haloperidol. When medication is necessary for delirium, American Psychiatric Association (APA) guidelines consider low-dose haloperidol as first-line treatment (see ***Related Resources, page 63***). Recommended dosage is 1 to 2 mg (0.25 to 0.5 mg for the elderly) every 4 hours as needed.

Adding oral or IV lorazepam (0.5 to 1 mg every 1 to 2 hours) to haloperidol may help rapidly sedate the agitated delirious patient and minimize the risk of EPS associated with haloperidol.[1] Avoid benzodiazepine monotherapy unless delirium is related to alcohol or benzodiazepine withdrawal.

Chlorpromazine. We have successfully used oral or IV chlorpromazine (12.5 to 50 mg every 4 to 12 hours) instead of haloperidol plus lorazepam when increased sedation was required, especially:

- in the ICU, where close blood pressure monitoring was feasible
- for severe agitation in terminally ill patients to decrease distress for the patient, family and staff.

Monitor chlorpromazine's anticholinergic and hypotensive side effects, particularly in elderly patients. Its anticholinergic effects could worsen delirium, but we are not aware of any studies or case reports supporting that clinical outcome.

Atypical antipsychotics also may be used to treat delirium, as supported by the literature. Recommended dosing, available routes administration routes, and clinical comments are summarized in ***Table 3 (page 57)***.[23]

Managing adverse effects

Reassess patients frequently during a delirium episode to adjust the antipsychotic dose, search for underlying causes, and monitor for side effects (***Table 4, page 62***). In frail elderly patients, start with approxi-

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Table 3

Recommended antipsychotic dosing for delirium*

Antipsychotic	Dosage	Route†	Comment
Typical agents			
Haloperidol	Initial: 0.5 to 1 mg Range: 0.5 to 2 mg every 2 to 12 hours	Oral, IV, SC, IM	'First choice' for delirium when antipsychotic treatment is needed (per APA guidelines)
Chlorpromazine	Initial: 12.5 to 25 mg Range: 12.5 to 50 mg every 4 to 12 hours	Oral, IV, IM	Alternative to haloperidol plus lorazepam when increased sedation is needed
Atypical agents			
Risperidone	Initial: 0.25 to 1 mg Range: 0.25 to 2 mg/d	Oral	Risk of sedation and orthostatic hypotension at higher doses
Olanzapine	Initial: 2.5 to 5 mg nightly Range: 2.5 to 10 mg/d	Oral	Sedation (a potential limiting factor) may be beneficial for hyperactive delirium
Quetiapine	Initial: 25 to 50 mg Range: 25 to 200 mg/d, usually divided into 2 daily doses	Oral	Sedation and orthostatic hypotension are dose-limiting factors
Ziprasidone	Initial: 20 mg bid Range: 20 to 160 mg/d, usually divided into 2 daily doses	Oral	Limited data in delirium because of concerns about QT interval prolongation in medically ill patients
Aripiprazole	Initial: 10 to 15 mg Range: 10 to 30 mg/d	Oral	'Dopamine stabilizing' effect might be preferable in hypoactive delirium

* For frail elderly patients, start with approximately one-half the suggested initial dose.
† Risperidone and aripiprazole are available in liquid formulations. Risperidone, olanzapine, and aripiprazole are available in orally disintegrating tablets.
APA: American Psychiatric Association; IM: intramuscular; IV: intravenous; SC: subcutaneous

Source: Reference 23

Clinical Point

In frail elderly patients, start with approximately one-half the usual recommended initial dose to reduce the risk of side effects

mately one-half the recommended initial dose to reduce the side effect risk.

Antipsychotics may not be appropriate in certain populations with delirium, particularly in patients with:

- dementia of Lewy body type or Parkinson's disease dementia
- stroke
- history of adverse reactions to antipsychotics.

Mortality risk. All atypicals carry a "black-box" warning of increased risk of death when treating behavioral disturbances in elderly patients with dementia-related psychosis. The FDA advisory is based on a meta-analysis by Schneider et al[2] of 17 placebo-controlled trials totaling 3,353 patients with Alzheimer's disease or dementia. Risk of death in the drug-treated patients was 1.6 to 1.7 times greater than in those who received placebo. Most deaths were associated with cardiovascular disease or infection (including pneumonia).

Although the FDA advisory did not apply to typical antipsychotics, Wang et al[3]—in a retrospective cohort of nearly 23,000 patients age >65—found statistically significant higher mortality rates with typical vs atypical antipsychotics. The increased mortality risk with the typical agents was seen whether or not patients had dementia. The greatest increases in risk occurred early in therapy and with relatively high dosages.

The mortality risk associated with short-term antipsychotic treatment in medically ill elderly patients is unknown. Untreated delirium may impose a greater risk of mor-

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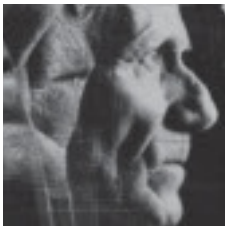

Table 4

Monitoring for antipsychotic side effects during delirium treatment

Side effects	How to monitor
EPS (parkinsonism, akathisia, dystonia)	Neurologic examination
Neuroleptic malignant syndrome	Neurologic examination, serum creatinine phosphokinase, serum prolactin
QT interval prolongation, torsades de pointes	ECG, serum potassium and magnesium, family history of QT prolongation
Metabolic syndrome (hyperglycemia, hyperlipidemia, weight gain)	Fasting blood glucose, lipid profile, weight, hemoglobin A1c
Anticholinergic symptoms (dry mouth, constipation)	History and physical examination

EPS: extrapyramidal symptoms

Clinical Point

Untreated delirium may pose a greater risk of morbidity and mortality than the risk associated with antipsychotics

bidity and mortality than the risk associated with antipsychotics, however. Until more evidence becomes available, we recommend that you try to use low antipsychotic doses, especially for the elderly.

EPS are more common with conventional antipsychotics but also can be associated with the atypicals—particularly with risperidone at doses higher than 4 to 6 mg/d. To minimize EPS risk, monitor delirium patients daily during antipsychotic treatment and identify populations at risk.

Neuroleptic malignant syndrome. Watch for NMS while treating medically ill patients with delirium. Symptoms include severe rigidity, hyperthermia, altered mental status, and autonomic dysfunction.

QT interval prolongation. A prolonged QT interval increases the risk of ventricular arrhythmias—such as torsades de pointes and ventricular fibrillation—that can lead to syncope, cardiac arrest, or sudden cardiac death. Among the atypicals, ziprasidone has been associated with the highest rates of QT interval prolongation, followed by quetiapine, risperidone, and olanzapine.[24] Thioridazine carries the greatest risk among the typical agents.[25]

When using antipsychotics for delirium, identify patients at risk for QT interval changes and monitor all patients during treatment. Risk factors include older age, female sex, preexisting heart disease, bradycardia, electrolyte abnormalities, and use of drugs that block potassium. APA guidelines recommend discontinuing antipsychotic therapy if QTc exceeds 450 msec or increases >25% from baseline.[1] Consult with a cardiologist when antipsychotic treatment is necessary despite QT prolongation.

Metabolic syndrome. Long-term use of atypical antipsychotics—particularly olanzapine—has been associated with metabolic dysregulation and increased risk of obesity and diabetes. In the absence of data on the atypicals' short-term effects on metabolism, we recommend careful monitoring for metabolic syndrome when using these agents, especially in patients with preexisting metabolic disturbances.[26]

Discontinuing antipsychotics

No evidence-based or expert consensus guidelines have addressed when or how to discontinue antipsychotic treatment of delirium. Several studies—including a randomized, controlled trial by our group[12]—used protocols that reflect expert clinician practice.

Antipsychotic therapy is initiated to control delirium's symptoms and is presumed to be needed until the causes have been identified or have resolved. Thus, antipsychotics are typically given in 3 phases:

Initial phase. Start antipsychotic therapy

to control delirium symptoms, usually by dose titration over the first 24 to 48 hours.

Maintenance. Continue the antipsychotic 7 to 10 days—typically at two-thirds to one-half the initial-phase dosage—to allow delirium causes to be identified and resolve.

Tapering/discontinuation. If delirium symptoms resolve, taper and discontinue the antipsychotic relatively slowly over 3 to 5 days to allow for rapid control should delirium symptoms re-emerge. Re-emergence suggests that new or unrecognized causes of delirium are present or identified causes have not resolved.

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Related Resources

- American Psychiatric Association. Treating delirium: a quick reference guide. www.psych.org/psych_pract/treatg/quick_ref_guide/DeliriumQRG_4-15-05.pdf.
- American Psychiatric Association. Guideline watch: practice guideline for the treatment of patients with delirium. www.psych.org/psych_pract/treatg/pg/Delirium.watch.pdf.
- American Psychosocial Oncology Society. Multidisciplinary training in psycho-oncology: delirium. www.apos-society.org/professionals/meetings-ed/webcasts/webcasts-multidisciplinary.aspx#.

Drug Brand Names

Aripiprazole • Abilify
Chlorpromazine • various
Haloperidol • various
Lorazepam • Ativan
Olanzapine • Zyprexa
Quetiapine • Seroquel
Risperidone • Risperdal
Ziprasidone • Geodon

Disclosures

Dr. Breitbart is a consultant to Cephalon and a speaker for Cephalon, Janssen Pharmaceutica, Purdue Pharma, Eli Lilly and Company, and Bristol-Myers Squibb.

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Clinical Point

Antipsychotic therapy is presumed to be needed for delirium symptoms until the causes have been identified or have resolved

Bottom Line

When choosing an antipsychotic for delirium, consider risks of EPS, sedation, anticholinergic effects, cardiac arrhythmias, and drug-drug interactions. Evidence for using short-term, low-dose antipsychotics for delirium is limited, but serious adverse events appear uncommon. In sick elderly patients, the mortality risk from untreated delirium may exceed the risk from short-term antipsychotic therapy.