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. 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. Similarly, a retrospective study of elderly patients taking antipsychotics found higher mortality rates associated with typical antipsychotics than with atypicals.

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)—particularly with dementia—but also occurs

William Breitbart, MD
Professor of psychiatry
Weill Medical College of Cornell University
Chief, psychiatry service
Department of psychiatry and behavioral sciences
Attending psychiatrist, Pain and Palliative Care Service
Memorial Sloan-Kettering Cancer Center
New York

Yesne Alici-Evcimen, MD
Geriatric psychiatry fellow
Department of psychiatry, section on geriatric psychiatry
University of Pennsylvania
Philadelphia

1,4-7
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. Elderly inpatients who develop delirium have an estimated mortality rate of 22% to 76% during that hospitalization. At the end of life, the prevalence of delirium may be as high as 85%.

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

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

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

Delirium is underdiagnosed and undertreated in medical settings, most likely because of its protean symptoms and fluctuating clinical findings. Neurologic abnormalities—including cortical and motor symptoms—also can occur.

Mortality risk. Delirium is an independent risk factor for mortality. 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.

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)
- 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 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 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 group¹² 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

<table>
<thead>
<tr>
<th>Recognizing delirium: Diagnostic clinical features*</th>
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<tbody>
<tr>
<td>Altered level of alertness and arousal</td>
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<tr>
<td>Rapidly fluctuating course</td>
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<tr>
<td>Attention disturbance</td>
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<tr>
<td>Increased or decreased psychomotor activity</td>
</tr>
<tr>
<td>Disturbance of sleep-wake cycle</td>
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<tr>
<td>Affective symptoms</td>
</tr>
<tr>
<td>Altered perceptions</td>
</tr>
<tr>
<td>Disorganized thinking and incoherent speech</td>
</tr>
<tr>
<td>Disorientation and memory impairment</td>
</tr>
</tbody>
</table>

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

### Table 2

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

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 delirium¹⁶ 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 al¹⁷ studied dopamine trans-
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.

**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. 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).

**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-
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. 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. 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 3**

**Recommended antipsychotic dosing for delirium**

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

* 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 dispersing tablets.
APA: American Psychiatric Association; IM: intramuscular; IV: intravenous; SC: subcutaneous

Source: Reference 23
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 group22—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.

### References

### Related Resources

### Drug Brand Names
- Aripiprazole - Abilify
- Chlorpromazine - various
- Haloperidol - various
- Lorazepam - Ativan
- Olanzapine - Zyprexa
- Quetiapine - Seroquel
- Risperidone - Risperdal
- Ziprasidone - Geodon

### Disclosures
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Dr. Alici-Evcimen reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

### 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.