Ms. B, age 48, is admitted to our hospital after overdosing on unknown amounts of amitriptyline, diphenhydramine, and laxatives. Three days after admission, the psychiatry service is consulted to assess her for “bipolar disorder.” Although Ms. B does not have a psychiatric history, her internist believes her pressured speech and psychomotor agitation warrant investigation.

During the initial psychiatric interview, Ms. B is disoriented, with fluctuating alertness and cognition. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)\(^1\) is positive for delirium. We perform a delirium workup while we start Ms. B on olanzapine, 5 mg/d orally and 5 mg intramuscular (IM) every 8 hours as needed.

Ms. B’s laboratory results (complete blood count, complete metabolic profile, urinalysis, chest roentgenogram, vitamin B12 level, blood alcohol level, urine drug screen, arterial blood gas, and head CT) are unremarkable except for her amitriptyline/nortriptyline level, which is in the toxic range. On physical examination, Ms. B’s heart rate and temperature are elevated, her pupils are dilated and sluggish, and her skin is hot and dry. Based on these findings, we determine that Ms. B’s delirium most likely is an anticholinergic syndrome from amitriptyline/diphenhydramine toxicity.\(^2\) We discontinue olanzapine after only 2 doses because of its potential anticholinergic effects.\(^3\)

In hospitalized patients, delirium is one of the most frequently encountered mental disorders, but because of its variable presentation the condition often is underrecognized and undertreated, which leads to longer hospitalizations and increased mortality.\(^4,5\) Ms. B’s case illustrates

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**Atypical antipsychotics for delirium: A reasonable alternative to haloperidol?**

Newer agents may offer similar efficacy with fewer adverse effects

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David R. Spiegel, MD  
Associate Professor of Clinical Psychiatry and Behavioral Sciences  
Director of Consultation-Liaison Services

David Ahlers, MD  
Psychiatry Resident

Grant Yoder, DO  
Psychiatry Resident

Nabeel Qureshi, MD  
Psychiatry Resident

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Department of Psychiatry and Behavioral Sciences  
Eastern Virginia Medical School  
Norfolk, VA
Antipsychotics for delirium

Clinical Point

Antipsychotics improve delirium symptoms even before underlying medical etiologies are treated

Table 1

Delirium: Diagnostic criteria

<table>
<thead>
<tr>
<th>Delirium describes a group of related disorders with variable clinical presentations and differing causation. Regardless of the etiology, all types of delirium share a set of common symptoms that include:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disturbances of consciousness and attention</strong></td>
</tr>
<tr>
<td>Changes in cognition such as memory deficit, language disturbance, or disorientation</td>
</tr>
<tr>
<td>Perceptual disturbances not better accounted for by dementia</td>
</tr>
<tr>
<td>Abrupt onset (usually hours to days)</td>
</tr>
<tr>
<td>Fluctuating symptoms throughout the course of the day</td>
</tr>
</tbody>
</table>

**Source:** Adapted from reference 6

the classical delirium presentation (Table 1), highlighting 2 hallmark features of the disorder: inattention and an acute fluctuating course. Unfortunately, delirium is a diverse disorder that may present with numerous nonclassical symptoms—including lethargy, emotionality, sleep irregularities, and neurologic abnormalities—in lieu of more commonly recognized symptoms.

In addition to recommending identifying and addressing the underlying acute illness, American Psychiatric Association guidelines suggest prescribing psychotropic medications to treat delirium symptoms. Antipsychotics are considered first-line pharmacotherapy because they have been shown to lower hospital mortality rates and improve delirium symptoms even before underlying medical etiologies are treated.

Haloperidol is the mainstay of delirium treatment. Compared with atypical antipsychotics in delirium treatment, haloperidol doses <3.5 mg/d have not been associated with an increase in extrapyramidal symptoms (EPS).

Although not devoid of side effects, atypical antipsychotics are an alternative to haloperidol. This article briefly summarizes the current evidence on the use of typicals for treating delirium.

**CASE CONTINUED**

**IM ziprasidone**

After reassessing our treatment options, we prescribe ziprasidone, 10 mg IM twice a day, and an additional 10 mg IM every 12 hours as needed. Ziprasidone's minimal anticholinergic and sedative effects seem favorable for Ms. B's delirium; however, this medication has several drawbacks, including IM administration, greater expense compared with intravenous haloperidol, and risk of adverse cardiac effects, specifically prolonged corrected QT (QTc) interval. Bioavailability of oral ziprasidone is markedly less than the IM preparation (~60% vs 100%, respectively), and oral bioavailability decreases to approximately 30% when taken without food. Given Ms. B's her current mental state, we feel that IM ziprasidone is a more reliable means to achieve therapeutic efficacy.

With respect to cardiac concerns, we evaluate Ms. B's predisposing and precipitating risk factors. Family members confirm that she had no cardiac history. We obtain baseline ECGs and continually monitor her QTc interval, which remained at <500 msec during ziprasidone treatment.

Ms. B tolerates ziprasidone and we note modest improvement in her mental status after 2 days of treatment; her vigilant-A portion of the CAM-ICU improves, but she still screens positive for delirium. During the next week Ms. B develops several medical comorbidities, including ileus, urinary tract infection, and methicillin-resistant *Staphylococcus aureus* infection. Despite these complications her mental status continues to improve. Within 6 days, Ms. B's attention and cognition improve dramatically. She is oriented and able to engage in medical decision-making, and she screens negative for delirium on the CAM-ICU. We begin to assess her for psychiatric disorders that may have contributed to her hospitalization.

**Evidence for antipsychotics**

**Haloperidol** has been the antipsychotic of choice for treating delirium symptoms. It is recommended by the Society of Critical Care Medicine and is regarded as safe, cost-effective, and efficacious for delirium despite a risk of dose-related EPS and potential cardiac conduction alterations.

**Risperidone** is not indicated for treating delirium but is one of the most extensively studied atypical antipsychotic alternatives to haloperidol. Evidence consisting pri-
A predominantly of case reports has illustrated the potential efficacy of risperidone in treating delirium (Table 2).\textsuperscript{10,15-19}

In 2004, Parellada et al\textsuperscript{17} observed significant mean improvements in all measures (Delirium Rating Scale [DRS], Mini-Mental State Exam [MMSE], positive subscale of the Positive and Negative Syndrome Scale [PANSS-P], and Clinical Global Impressions scale [CGI]) in 64 delirium patients treated with risperidone. In a 2004 double-blind trial of 28 delirium patients randomly assigned to risperidone or haloperidol, risperidone was effective but not significantly more efficacious than low-dose haloperidol for acute delirium treatment.\textsuperscript{18}

Advantages of using risperidone include its lack of anticholinergic effects. Potential side effects include dose-related EPS and weight gain, which were observed in patients with schizophrenia and other

### Table 2

**Risperidone for delirium: What the evidence says**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients/dosage</th>
<th>Peak clinical response</th>
<th>Results/adverse effects (AEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipahimalani et al, 1997\textsuperscript{15}</td>
<td>2 (age 14 and 60). Initial dose: 1 mg/d; maintenance dose: 2 mg/d</td>
<td>10 to 14 days</td>
<td>MMSE score increased. AEs: extrapyramidal symptoms (dystonia and cogwheeling)</td>
</tr>
<tr>
<td>Schwartz et al, 2002\textsuperscript{10}</td>
<td>11 (age range 14 to 74). Mean dose: 1.59 ± 0.8 mg/d</td>
<td>5.1 ± 4.3 days</td>
<td>CGI score decreased. No reported AEs</td>
</tr>
<tr>
<td>Horikawa et al, 2003\textsuperscript{16}</td>
<td>10 (mean age: 56.8; range: 22 to 81). Mean dose: 1.7 mg/d</td>
<td>7.1 days</td>
<td>DRS score decreased significantly in 80% of patients ($P = .03$). AEs: sleepiness (30%), mild drug-induced parkinsonism (10%)</td>
</tr>
<tr>
<td>Parellada et al, 2004\textsuperscript{17}</td>
<td>64 (mean age: 67.3 ± 11.4 years). Mean dose: 2.6 ± 1.7 mg/d</td>
<td>3 to 7 days</td>
<td>Effective in 90.6% of patients with significant decreases in DRS, PANSS-P, and CGI and increase in MMSE ($P &lt; .001$). AEs: drowsiness (3.1%), nausea (1.6%)</td>
</tr>
<tr>
<td>Hans et al, 2004\textsuperscript{18}</td>
<td>12 (mean age: 65.6). Mean dose: 1.02 mg/d</td>
<td>4 to 7 days</td>
<td>MDAS scores decreased significantly ($P &lt; .05$). No reported AEs</td>
</tr>
<tr>
<td>Bourgeois et al, 2005\textsuperscript{19}</td>
<td>1 (age 57). Initial dose: 8 mg/d; maintenance dose: 2 mg/d</td>
<td>9 days</td>
<td>MMSE score increased. No reported AEs</td>
</tr>
</tbody>
</table>

**Clinical Point**

In a small double-blind, randomized trial, risperidone was effective but not significantly more so than low-dose haloperidol

### Table 3

**Olanzapine may have a role in treating delirium symptoms**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients/dosage</th>
<th>Peak clinical response</th>
<th>Results/adverse effects (AEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipahimalani et al, 1998\textsuperscript{22}</td>
<td>11 (mean age: 63.5 ± 23.2 years). Mean dose: 8.2 ± 3.4 mg/d</td>
<td>6.8 ± 3.5 days</td>
<td>Marked decrease (&gt;50%) in DRS score for 5 patients. No reported AEs</td>
</tr>
<tr>
<td>Breitbart et al, 2002\textsuperscript{23}</td>
<td>79 (mean age: 60.6 ± 17.3 years; range: 19 to 89). Initial dose: 3 ± 0.14 mg/d; mean dose: 4.6 to 6.3 mg/d</td>
<td>2 to 7 days</td>
<td>MDAS decreased significantly ($P &lt; .001$), with 76% of patients’ delirium reaching resolution (MDAS ≤10). AEs: sedation (30%)</td>
</tr>
<tr>
<td>Hu et al, 2004\textsuperscript{24}</td>
<td>74 (mean age: 74). Mean dose: 1.25 to 2 mg/d</td>
<td>2.78 ± 1.85 days</td>
<td>DRS score decreased significantly ($P &lt; .01$) in 72.2% of patients. AEs: drowsiness (18.9%), dystonia (2.7%), dry mouth (2.7%)</td>
</tr>
</tbody>
</table>

DRS: Delirium Rating Scale; MDAS: Memorial Delirium Assessment Scale
Antipsychotics for delirium

Clinical Point
Quetiapine reduced delirium duration and agitation in a small double-blind randomized trial of adult ICU patients.

Evidence suggests quetiapine could reduce delirium symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients/dosage</th>
<th>Peak clinical response</th>
<th>Results/adverse effects (AEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al, 2002</td>
<td>N=11 (age range: 19 to 91). Mean dose: 211.4 mg/d</td>
<td>6.5 days</td>
<td>Decrease in DRS score (&gt;50% reduction in global delirium symptoms) for 10 patients. AEs: sedation</td>
</tr>
<tr>
<td>Al-Samarrai et al, 2003</td>
<td>N=2 (age 50 and 52). Mean dose: 200 to 400 mg/d</td>
<td>2 to 4 days</td>
<td>No specific rating scale used but clinical reduction in agitation and improvement in cognition were reported. AEs: drowsiness</td>
</tr>
<tr>
<td>Sasaki et al, 2003</td>
<td>N=12 (mean age: 67.3 ± 14.8 years). Mean dose: 44.9 ± 31.0 mg/d</td>
<td>4.8 ± 3.5 days</td>
<td>Decrease in DRS score and remission of delirium for all patients. Significant increase in MMSE (P = .0256). No reported AEs</td>
</tr>
<tr>
<td>Devlin et al, 2010</td>
<td>N=18 (adult ICU patients). Initial dose: 100 mg/d</td>
<td>36 to 87 hours</td>
<td>Significantly shorter time to first resolution of delirium and duration of delirium compared with placebo. AEs: somnolence</td>
</tr>
</tbody>
</table>

DRS: Delirium Rating Scale; ICU: intensive care unit; MMSE: Mini-Mental State Exam

Limited data support ziprasidone and aripiprazole for treating delirium

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients/dosage</th>
<th>Peak clinical response</th>
<th>Results/adverse effects (AEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leso et al, 2002</td>
<td>N=1 (age 34). Initial dose: 40 mg/d; maintenance dose: 100 mg/d</td>
<td>21 days</td>
<td>DRS score decreased from 26 to 14. AEs: 8.4% increase in QTc interval</td>
</tr>
<tr>
<td>Young et al, 2004</td>
<td>N=1 (age 47). Initial dose: 20 mg IV bolus, followed by an oral taper over 7 days.</td>
<td>7 days</td>
<td>No specific rating scale was used but dramatic improvement in patient's restlessness was reported. No AEs reported</td>
</tr>
</tbody>
</table>

Aripiprazole

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients/dosage</th>
<th>Peak clinical response</th>
<th>Results/adverse effects (AEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alao et al, 2006</td>
<td>N=2 (age 62 and 37). Mean dose: 15 and 30 mg/d</td>
<td>2 to 7 days</td>
<td>Patient 1: DRS score decreased from 28 to 6 and MMSE score increased from 5 to 28. Patient 2: DRS score decreased from 18 to 6 and MMSE score increased from 7 to 27. No AEs reported</td>
</tr>
<tr>
<td>Straker et al, 2006</td>
<td>N=14 (age range: 18 to 85). Mean dose: 8.9 mg/d</td>
<td>2 to 14 days</td>
<td>12 of 14 patients had a ≥50% decrease in DRS-R-98. AEs: 3 patients had prolonged QTc interval</td>
</tr>
</tbody>
</table>

DRS: Delirium Rating Scale; DRS-R-98: Delirium Rating Scale–Revised-98; MMSE: Mini-Mental State Exam

psychotic disorders and dementia-related behavioral disorders.\(^{20,21}\)

Olanzapine. Much like risperidone, olanzapine’s use in delirium is relatively well described in the literature (\textit{Table 3, page 39}).\(^{22-24}\)

In a randomized, placebo-controlled study comparing olanzapine with haloperidol, 175 patients were treated for 7 days with olanzapine, haloperidol, or placebo. Olanzapine and haloperidol showed significantly greater DRS score improvement than placebo.\(^{24}\) There was no difference between olanzapine and haloperidol outcomes; however, olanzapine showed significant improvement by days 2 and 3 compared with haloper-
In vitro, desvenlafaxine does not inhibit or induce the CYP isozymes based on in vitro data. Drugs that inhibit CYP isozymes (CYP1A2, 2C9, 2C19, 2D6, 3A4) and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Anticoagulant effects, including increased bleeding, have been observed when SSRI and SNRI coadministration is continued with warfarin. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued. Ethanol - A clinical study has shown that desvenlafaxine does not increase the risk of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq. Potential for Other Drugs to Affect Desvenlafaxine - Drugs metabolized by CYP3A4 (ketoconazole) should be carefully monitored when Pristiq is initiated or discontinued. Other Drugs to Affect Desvenlafaxine - Drugs metabolized by CYP3A4 (ketoconazole) should be carefully monitored when Pristiq is initiated or discontinued.

Inhibitors of CYP3A4 (ketoconazole)

Other Drugs to Affect Desvenlafaxine - Drugs metabolized by CYP3A4 (ketoconazole) should be carefully monitored when Pristiq is initiated or discontinued. Other Drugs to Affect Desvenlafaxine - Drugs metabolized by CYP3A4 (ketoconazole) should be carefully monitored when Pristiq is initiated or discontinued.

Quetiapine. Case reports have suggested quetiapine is effective for delirium (Page 4, page 40). In a prospective, open-label trial, Sasaki et al. treated 12 delirium patients with a single bedtime dose of quetiapine. All patients achieved remission within several days of beginning quetiapine, and the drug was well tolerated with no detected EPS or excessive sedation.

In 2010 Devlin et al. reported on the efficacy and safety of quetiapine in a prospective double-blind, placebo-controlled study of 36 adult ICU patients. Compared with those receiving placebo, patients taking quetiapine had a statistically significant shorter time to first resolution of delirium, reduced duration of delirium, and less agitation as measured by the Sedation-Agitation Scale. Mortality, ICU length of stay, and incidence of QoL improvement did not differ, but patients treated with quetiapine were more likely to be discharged home or to rehabilitation and to have more comorbidity. Quetiapine’s side effect profile includes a low occurrence of EPS, sedation, and dose-related anticholinergic effects.

Ziprasidone. The literature on ziprasidone for delirium so far is limited to a few anecdotal case reports (Page 5, page 40). In 2002, Leso and Schwartz successfully used ziprasidone to treat delirium in a patient with human immunodeficiency virus and cryptococcal meningitis. Ziprasidone was chosen for its lack of sedating effects and low EPS risk. The patient experienced significant clearing of his delirium and lowering of his DRS score. Ziprasidone eventually was discontinued because a

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dol. Haloperidol was associated with a significantly higher rate of dystonia compared with olanzapine.

Olanzapine carries a risk of anticholinergic effects. This can be a drawback, especially in patients such as Ms. B whose delirium has an anticholinergic component. Olanzapine is available in an IM formulation, which can be an advantage when addressing agitation and medical comorbidities of delirium.
Antipsychotics for delirium

Clinical Point
A medication’s anticholinergic burden needs to be weighed against its potential nonanticholinergic adverse effects and other factors.

Risk factors for antipsychotic-induced QT interval prolongation and torsades de pointes*

<table>
<thead>
<tr>
<th>Pharmacologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic selection</td>
</tr>
<tr>
<td>Drug interaction (QT-prolonging agents)</td>
</tr>
<tr>
<td>Drug interaction (slow metabolism by cytochrome P450 inhibitors of 2D6, 3A4, 1A2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonpharmacologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age (&gt;65)</td>
</tr>
<tr>
<td>Bradycardia</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
</tr>
<tr>
<td>Hepatic/renal dysfunction</td>
</tr>
<tr>
<td>Genetic predisposition</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
</tbody>
</table>

Screening (major risk factors)
- Structural cardiac disease
- Congenital long QT syndrome
- Family history of sudden cardiac death
- Previous episodes of drug-induced QT prolongation or torsades de pointes

*Serial electrocardiograms are recommended for patients with a major risk factor or multiple pharmacologic/nonpharmacologic risk factors

Source: References 11,35-37

fluctuating QTc interval associated with co-morbid electrolyte imbalances—a potential drawback to ziprasidone.

In the case of Ms. B, ziprasidone appeared to be efficacious; however, improvement in her medical condition, rather than ziprasidone treatment, is the most likely explanation for the resolution of her delirium symptoms.

Aripiprazole. Alao et al reported on 2 delirium patients treated with 30 mg and 15 mg aripiprazole; improvement was monitored using the MMSE and DRS (Table 5, page 40). In both cases, confusion, disorientation, and agitation improved within 7 days of treatment. In the first case, the patient’s MMSE score improved from 5 to 28 and his DRS score decreased from 28 to 6. The second patient’s MMSE score improved from 7 to 27 and her DRS score went from 18 to 6.

Straker et al reported on 14 delirium patients treated with aripiprazole. Twelve patients had a ≥50% reduction in DRS, Revised-98 scores, and 13 showed improvement on CGI scores. The rate of adverse side effects was low. Three patients had prolonged QTc interval, but no patients developed arrhythmia or discontinued aripiprazole.

Anticholinergic activity
Decreased acetylcholine activity (AA) is suspected in delirium pathogenesis. By extension of this theory, medications that block muscarinic receptors could worsen delirium. Haloperidol, risperidone, and ziprasidone have negligible or no AA, as reported in atropine equivalents. Quetiapine and olanzapine have mild (0.5 to 5 pmol/mL) and moderate (5 to 15 pmol/mL) dose-related AA, respectively. For example, olanzapine, 5 mg/d, has roughly the same AA as quetiapine, 300 mg/d, whereas olanzapine, 10 mg/d, has about the same AA as quetiapine, 600 mg/d.

Although we used this evidence, in part, to select an atypical antipsychotic for Ms. B, this model should be used only to estimate the possible anticholinergic burden associated with a specific medication or combination. The risk of anticholinergic burden needs to be considered along with a medication’s potential nonanticholinergic adverse effects and the patient’s overall clinical history (eg, past sensitivity to anticholinergic agents, memory complaints, effectiveness of an agent, concomitant medications, disease state, adherence concerns). For example, an atypical antipsychotic that is potently anti-histaminergic and therefore sedating could be beneficial when treating an agitated delirium patient. Establishing the presence of a risk of anticholinergic burden cannot be equated with the presence of anticholinergic toxicity, because the exact relationship between AA and cognitive performance is still unknown.

Cardiovascular safety
The most common cardiovascular effects of atypical antipsychotics are tachycardia,
hypotension (usually mild), and prolongation of QTc interval. For example, haloperidol, 15 mg/d, was found to increase mean QTc by 7 msec, with a reported odds ratio ranging from 2.2 to 6.1 for ventricular dysrhythmia and sudden cardiac death, although risk may be more strongly associated with high-dose, IV haloperidol.

QTc interval prolongation warrants concern because it suggests that patients may be predisposed to torsades de pointes (TdP). Conventional antipsychotics—especially phenothiazines—have the highest risk of inducing TdP. One review concluded that compared with other antipsychotics, chlorpromazine, pimozide, thioridazine, and the atypical clozapine have a higher risk of cardiac arrhythmias and sudden cardiac death. Another review found cases of TdP with haloperidol, ziprasidone, olanzapine, and thioridazine. When prescribing an antipsychotic, consider both pharmacologic and nonpharmacologic risk factors, including preexisting cardiovascular disease, female sex, hepatic insufficiency, electrolyte abnormalities, stimulant drug abuse, and genetic predisposition (Table 6).

References

Drug Brand Names
- Amitriptyline: Elavil
- Nortriptyline: Aventyl
- Atropine: Sal-Tropine
- Chlorpromazine: Thorazine
- Clozapine: Clozaril
- Diphenhydramine: Benadryl
- Haloperidol: Haldol
- Aripiprazole: Abilify
- Olanzapine: Zyprexa
- Pimozide: Orap
- Quetiapine: Seroquel
- Risperidone: Risperdal
- Thioridazine: Mellaril
- Ziprasidone: Geodon

Disclosures
Dr. Spiegel is a speaker for AstraZeneca, Pfizer, Inc., and Janssen Pharmaceuticals. Drs. Ahlers, Yoder, and Qureshi report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Related Resource
Antipsychotics for delirium

Although haloperidol is the ‘gold standard’ for symptomatic treatment of delirium, atypical antipsychotics may be equally effective without haloperidol’s undesirable side effects. Most of the evidence that supports using atypical antipsychotics to treat delirium comes from case reports and open trials. Potential efficacy needs to be weighed against the risk of adverse effects, including extrapyramidal symptoms and cardiac conduction abnormalities.