

Atypical antipsychotics for delirium: A reasonable alternative to haloperidol?

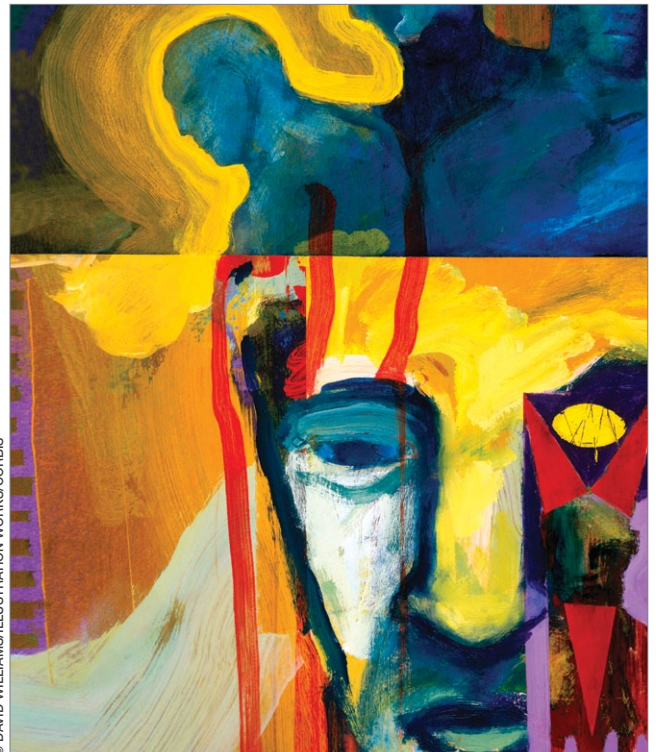
Newer agents may offer similar efficacy with fewer adverse effects

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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Antipsychotics for delirium

Clinical Point

Antipsychotics improve delirium symptoms even before underlying medical etiologies are treated

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Table 1 Delirium: Diagnostic criteria

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:

Disturbances of consciousness and attention

Changes in cognition such as memory deficit, language disturbance, or disorientation

Perceptual disturbances not better accounted for by dementia

Abrupt onset (usually hours to days)

Fluctuating symptoms throughout the course of the day

Source: Adapted from reference 6

the classical delirium presentation (*Table 1*),⁶ highlighting 2 hallmark features of the disorder: inattention and an acute fluctuating course.⁴ 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.^{4,5}

In addition to recommending identifying and addressing the underlying acute illness, American Psychiatric Association guidelines suggest prescribing psychotropic medications to treat delirium symptoms.^{5,7} Antipsychotics are considered first-line pharmacotherapy because they have been shown to lower hospital mortality rates⁸ and improve delirium symptoms even before underlying medical etiologies are treated.⁵ Haloperidol is the mainstay of delirium treatment.⁸ Compared with atypical antipsychotics in delirium treatment, haloperidol doses <3.5 mg/d have not been associated with an increase in extrapyramidal symptoms (EPS).⁹

Although not devoid of side effects, atypical antipsychotics are an alternative to haloperidol.^{8,10} This article briefly summarizes the current evidence on the use of atypicals 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 effects³ 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.¹¹ 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.¹² Given Ms. B's her current mental state, we feel that IM ziprasidone is a more reliable means to achieve therapeutic efficacy.¹³

With respect to cardiac concerns, we evaluate Ms. B's predisposing and precipitating risk factors.¹¹ 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 Medicine⁷ and is regarded as safe, cost-effective, and efficacious for delirium⁵ despite a risk of dose-related EPS and potential cardiac conduction alterations.^{5,14}

Risperidone is not indicated for treating delirium but is one of the most extensively studied atypical antipsychotic alternatives to haloperidol. Evidence consisting pri-

Table 2

Risperidone for delirium: What the evidence says

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

CGI: Clinical Global Impressions scale; DRS: Delirium Rating Scale; MDAS: Memorial Delirium Assessment Scale; MMSE: Mini-Mental State Exam; PANSS-P: positive subscale of the Positive and Negative Syndrome Scale

Table 3

Olanzapine may have a role in treating delirium symptoms

Study	Patients/dosage	Peak clinical response	Results/adverse effects (AEs)
Sipahimalani et al, 1998 ²²	N=11 (mean age: 63.5 ± 23.2 years). Mean dose: 8.2 ± 3.4 mg/d	6.8 ± 3.5 days	Marked decrease (>50%) in DRS score for 5 patients. No reported AEs
Breitbart et al, 2002 ²³	N=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	2 to 7 days	MDAS decreased significantly (<i>P</i> < .001), with 76% of patients' delirium reaching resolution (MDAS ≤10). AEs: sedation (30%)
Hu et al, 2004 ²⁴	N=74 (mean age: 74). Mean dose: 1.25 to 2 mg/d	2.78 ± 1.85 days	DRS score decreased significantly (<i>P</i> < .01) in 72.2% of patients. AEs: drowsiness (18.9%), dystonia (2.7%), dry mouth (2.7%)

DRS: Delirium Rating Scale; MDAS: Memorial Delirium Assessment Scale

marily of case reports has illustrated the potential efficacy of risperidone in treating delirium (Table 2).^{10,15-19}

In 2004, Parellada et al¹⁷ 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.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

Clinical Point

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



Antipsychotics for delirium

Clinical Point

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

Table 4

Evidence suggests quetiapine could reduce delirium symptoms

Study	Patients/dosage	Peak clinical response	Results/adverse effects (AEs)
Schwartz et al, 2002 ¹⁰	N=11 (age range: 19 to 91). Mean dose: 211.4 mg/d	6.5 days	Decrease in DRS score (>50% reduction in global delirium symptoms) for 10 patients. AEs: sedation
Al-Samarrai et al, 2003 ²⁵	N=2 (age 50 and 52). Mean dose: 200 to 400 mg/d	2 to 4 days	No specific rating scale used but clinical reduction in agitation and improvement in cognition were reported. AEs: drowsiness
Sasaki et al, 2003 ²⁶	N=12 (mean age: 67.3 ± 14.8 years). Mean dose: 44.9 ± 31.0 mg/d	4.8 ± 3.5 days	Decrease in DRS score and remission of delirium for all patients. Significant increase in MMSE ($P = .0256$). No reported AEs
Devlin et al, 2010 ²⁷	N=18 (adult ICU patients). Initial dose: 100 mg/d	36 to 87 hours	Significantly shorter time to first resolution of delirium and duration of delirium compared with placebo. AEs: somnolence

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

Table 5

Limited data support ziprasidone and aripiprazole for treating delirium

Study	Patients/dosage	Peak clinical response	Results/adverse effects (AEs)
Ziprasidone			
Leso et al, 2002 ²⁸	N=1 (age 34). Initial dose: 40 mg/d; maintenance dose: 100 mg/d	21 days	DRS score decreased from 26 to 14. AEs: 8.4% increase in QTc interval
Young et al, 2004 ²⁹	N=1 (age 47). Initial dose: 20 mg IV bolus, followed by an oral taper over 7 days.	7 days	No specific rating scale was used but dramatic improvement in patient's restlessness was reported. No AEs reported
Aripiprazole			
Aiao et al, 2006 ³⁰	N=2 (age 62 and 37). Mean dose: 15 and 30 mg/d	2 to 7 days	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
Straker et al, 2006 ³¹	N=14 (age range: 18 to 85). Mean dose: 8.9 mg/d	2 to 14 days	12 of 14 patients had a ≥50% decrease in DRS-R-98. AEs: 3 patients had prolonged QTc interval

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 (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 haloperi-

continued on page 43

voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: *Skin and subcutaneous tissue disorders* – Angioedema. **DRUG INTERACTIONS: Central Nervous System (CNS)-Active Agents**—The risk of using Pristiq in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Pristiq is taken in combination with other CNS-active drugs [see *Warnings and Precautions* (5.13)]. **Monoamine Oxidase Inhibitors (MAOIs)**—Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to Pristiq (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI [see *Contraindications* (4.2)]. **Serotonergic Drugs**—Based on the mechanism of action of Pristiq and the potential for serotonin syndrome, caution is advised when Pristiq is coadministered with other drugs that may affect the serotonergic neurotransmitter systems [see *Warnings and Precautions* (5.2)]. **Drugs that Interfere with Hemostasis (eg, NSAIDs, Aspirin, and Warfarin)**—Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake 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. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered 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 impairment 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-Inhibitors of CYP3A4 (ketoconazole)**—CYP3A4 is a minor pathway for the metabolism of Pristiq. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq. **Inhibitors of other CYP enzymes**—Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of Pristiq. **Potential for Desvenlafaxine to Affect Other Drugs—Drugs metabolized by CYP2D6 (desipramine)**—*In vitro* studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug. **Drugs metabolized by CYP3A4 (midazolam)**—*In vitro*, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug. **Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9, and 2C19**—*In vitro*, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes. **P-glycoprotein Transporter**—*In vitro*, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. **Electroconvulsive Therapy**—There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **USE IN SPECIFIC POPULATIONS: Pregnancy**—Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. **Teratogenic effects—Pregnancy Category C**—There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks. **Non-teratogenic effects**—Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see *Warnings and Precautions* (5.2)]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [see *Dosage and Administration* (2.2)]. **Labor and Delivery**—The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. **Nursing Mothers**—Desvenlafaxine (O-desmethylenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, a decision should be made whether or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer Pristiq to breastfeeding women if the expected benefits outweigh any possible risk. **Pediatric Use**—Safety and effectiveness in the pediatric population have not been established [see *Box Warning and Warnings and Precautions* (5.1)]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use**—Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term, placebo-controlled studies, there was a higher incidence of systolic orthostatic hypotension in patients ≥65 years of age compared to patients <65 years of age treated with Pristiq [see *Adverse Reactions* (6)]. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.6)]. If Pristiq is poorly tolerated, every other day dosing can be considered. SSRIs and SNRIs, including Pristiq, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see *Warnings and Precautions* (5.12)]. Greater sensitivity of some older individuals cannot be ruled out. **Renal Impairment**—In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.6) in the full prescribing information]. **Hepatic Impairment**—The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. The recommended dose in patients with hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended [see *Clinical Pharmacology* (12.6)]. **OVERDOSAGE: Human Experience with Overdosage**—There is limited clinical experience with desvenlafaxine succinate overdose in humans. In premarketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the *Overdosage* section of the venlafaxine package insert. In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdose may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdose, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear. Prescriptions for Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Management of Overdosage**—Treatment should consist of those general measures employed in the management of overdose with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR®). This brief summary is based on Pristiq Prescribing Information W10529C009, revised September 2009.

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.

Quetiapine. Case reports have suggested quetiapine is effective for delirium (*Table 4, page 40*).^{10,25-27} In a prospective, open-label trial, Sasaki et al²⁶ 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 al²⁷ 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 QTc prolongation did not differ, but patients treated with quetiapine were more likely to be discharged home or to rehabilitation and to have more somnolence. Quetiapine's side effect profile includes a low occurrence of EPS, sedation, and dose-related anticholinergic effects.²⁵

Ziprasidone. The literature on ziprasidone for delirium so far is limited to a few anecdotal case reports (*Table 5, page 40*).²⁸⁻³¹ In 2002, Leso and Schwartz²⁸ 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



Antipsychotics for delirium

Clinical Point

A medication's anticholinergic burden needs to be weighed against its potential nonanticholinergic adverse effects and other factors

Table 6

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

Pharmacologic

Antipsychotic selection
Drug interaction (QT-prolonging agents)
Drug interaction (slow metabolism by cytochrome P450 inhibitors of 2D6, 3A4, 1A2)

Nonpharmacologic

Advanced age (>65)
Bradycardia
Hypokalemia
Hypomagnesemia
Hepatic/renal dysfunction
Genetic predisposition
Female sex

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 comorbid 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 al³⁰ 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).²⁸⁻³¹ 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 al³¹ 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.³² 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.^{32,33}

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 antihistaminergic 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.^{32,33}

Cardiovascular safety

The most common cardiovascular effects of atypical antipsychotics are tachycardia,

hypotension (usually mild), and prolongation of QTc interval.³⁴ 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,³⁵ although risk may be more strongly associated with high-dose, IV haloperidol.³⁶

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.¹¹ Another review found cases of TdP with haloperidol, ziprasidone, olanzapine, and thioridazine.³⁷ When prescribing an antipsychotic, consider both pharmacologic and nonpharmacologic risks factors, including preexisting cardiovascular disease, female sex, hepatic insufficiency, electrolyte abnormalities, stimulant drug abuse,³⁶ and genetic predisposition (Table 6).^{11,35-37}

Related Resource

• Stern TA, Celano CM, Gross AF, et al. The assessment and management of agitation and delirium in the general hospital. *Prim Care Companion J Clin Psychiatry* 2010;12(1):e1–e11. www.psychiatrist.com/private/pccpdf/article_wrapper.asp?art=2010/09r00938yel/09r00938yel.htm.

Drug Brand Names

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

Disclosures

Dr. Spiegel is a speaker for AstraZeneca, Pfizer, Inc., and Janssen Pharmaceuticals.

Dr. Ahlers, Yoder, and Qureshi report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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continued

Clinical Point

Haloperidol increases QTc interval and may increase risk of ventricular dysrhythmia and sudden cardiac death

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Current PSYCHIATRY e-News **DEPRESSION UPDATE**

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Editor's note

Depression can adversely impact younger individuals in multiple ways. Green et al performed a meta-analysis demonstrating that untreated depression significantly increased the relative risk of preterm birth and low birth weight, which are leading causes of neonatal, infant, and childhood morbidity, mortality, and developmental impairment and disabilities. Richardson et al observed that higher scores (>11) on the Patient Health Questionnaire were highly sensitive and specific in detecting depression in adolescents and significantly correlated with increased functional impairment and psychosocial problems. In a naturalistic follow-up of adolescents who recovered from their acute major depressive episode with fluoxetine, cognitive-behavioral therapy, or both, almost half experienced a recurrence (female, 67%; male, 53%).

Two studies considered the expanding role of therapeutic remission. Janicak et al observed that a 63% remission rate over 6 months in 60 patients whose major depression was acutely responsive to transcranial magnetic stimulation (TMS) and then maintained on antidepressant monotherapy and adjunctive TMS when needed (8 patients). Finally, the first sham-controlled trial of deep brain stimulation for the nucleus accumbens in refractory obsessive-compulsive disorder patients also noted a robust and durable improvement in both residual depressive and anxiety symptoms. In improvement in mood within seconds to days for observations and weeks for completion. —Philip G. Janicak, MD, Professor of Psychiatry, Rush University Medical Center, Chicago, IL

Depression during pregnancy increase risk of adverse birth outcomes

Gene NK, et al. *Arch Gen Psychiatry*. 2010;67(10):1022-1024

A meta-analysis of 29 prospective studies looked for a possible link between maternal depression and adverse birth outcomes, including preterm birth (<37 weeks' gestation), low birth weight (<3,500 g), and intrauterine growth restriction (<10th percentile for gestational age). Researchers found that women with depression during pregnancy are at increased risk for preterm birth and low birth weight, although the magnitude of the effect varies depending on how depression was measured, country location, and US socioeconomic status.

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Patient Health Questionnaire-9 effectively screens adolescents for depression

Richardson LP, et al. *Psychiatry*. 2010. Epub ahead of print.

Researchers who administered the Patient Health Questionnaire-9 (PHQ-9) to screen 42 adolescents aged 13 to 17 for depression found a PHQ-9 score of 10 had a sensitivity of 90% and a specificity of 78% for detecting those who met DSM-IV-TR criteria for major depression. The cutoff point of 11 was optimal for maximizing sensitivity without loss of specificity. Higher PHQ-9 scores were significantly correlated with increased functional impairment and psychosocial problems.

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Recurrence after recovery is common among depressed adolescents

Corey J, et al. *Arch Gen Psychiatry*. 2010. Epub ahead of print.

In a 2-year longitudinal follow-up study, researchers evaluated outcomes of 86 male and 116 female adolescents with major depressive disorder (MDD) randomized to short-term fluoxetine, cognitive-behavioral therapy, a combination of both, or placebo. Almost 60 participants (68%) recovered from their acute MDD episode but 58.4% had a recurrence, defined as a new episode of MDD after recovery. Recurrence was significantly more common among females (57%) to males (53%). **Read more**

Transcranial magnetic stimulation may help prevent depressive relapse

Janicak PG, et al. *Arch Gen Psychiatry*. 2010;67(10):1019-1020

A naturalistic 6-week study followed 60 patients with major depressive disorder (MDD) who responded to a 6-week course of transcranial magnetic stimulation (TMS) and were maintained on antidepressant monotherapy. TMS was administered if patients met criteria for symptoms worsening (change of 2 or more on the Clinical Global Impressions-Severity scale for 2 consecutive weeks). Thirty-eight patients met criteria for symptom worsening; of these, 22 (58%) experienced improved symptoms with adjunctive TMS. **Read more**

Deep brain stimulation improves depressive symptoms in OCD patients

Deep D, et al. *Arch Gen Psychiatry*. 2010;67(10):1020-1021

A small double-blind study randomly assigned 16 patients with treatment-refractory obsessive-compulsive disorder (OCD) to receive bilateral deep brain stimulation (DBS) of the nucleus accumbens or sham stimulation. In addition to experiencing significant improvements in OCD symptoms, subjects who underwent DBS had significantly decreased

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Antipsychotics for delirium

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Bottom Line

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.