REVIEW

CME CREDIT ***LEARNING OBJECTIVE:*** Readers will prescribe antipsychotic drugs judiciously to manage delirium in hospitalized patients

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Delirium in hospitalized patients: Risks and benefits of antipsychotics

ABSTRACT

Consensus panel guidelines advocate for the judicious use of antipsychotic drugs to manage delirium in hospitalized patients when nonpharmacologic measures fail and the patient is in significant distress from symptoms, poses a safety risk to self or others, or is impeding essential aspects of his or her medical care. Here, we review the use of haloperidol, olanzapine, quetiapine, risperidone, and aripiprazole for this purpose.

KEY POINTS

Delirium is common in hospitalized patients and often leads to loss of independence and nursing-home placement.

The first-line treatment is to identify and address predisposing factors, provide supportive care, and manage symptoms through behavioral strategies.

Most antipsychotic medications can prolong the QT interval and thus pose a risk for torsades de pointes. The effect is greatest with intravenous haloperidol and least with aripiprazole.

Lacking head-to-head trials of antipsychotics, we suggest selecting the drug based on its pharmacologic properties and the patient's clinical context.

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Delirium is common in hospitalized patients and contributes to healthcare costs and poor patient outcomes, including death. Its diagnosis and management remain clinically challenging. Although consensus panel guidelines recommend antipsychotic medications to treat delirium when conservative measures fail, few head-to-head trials have been done to tell us which antipsychotic drug to select, and antipsychotic use poses risks in the elderly.

Here, we review the risks and benefits of using antipsychotic drugs to manage delirium and describe an approach to selecting and using 5 commonly used antipsychotics.

SCOPE OF THE PROBLEM

Delirium is common and serious, affecting 11% to 42% of patients hospitalized on general medical wards.[1] The burden to the public and individual patient is extremely high. Delirium has been found to result in an additional $16,303 to $64,421 per delirious patient per year, with a subsequent total 1-year health-attributable cost between $38 billion and $152 billion in the United States.[2] Furthermore, many patients who become delirious in the hospital lose their independence and are placed in long-term care facilities.[3]

Although delirium was originally thought to be a time-limited neurocognitive disorder, recent evidence shows that it persists much longer[4] and that some patients never return to their previous level of function, suggesting that a single episode of delirium can significantly alter the course of an underlying dementia with the dramatic initiation of cognitive decline.[3] Most alarmingly, delirium is associated with an increased rate of death.[1]

DSM-5 DEFINITION

According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5),[5] delirium is a neurocognitive disorder characterized by the acute onset of disturbance in attention, awareness, and cognition that fluctuates in severity throughout the day and is the direct physiologic consequence of another medical condition. The cognitive impairment seen in delirium is typically global and can affect memory, orientation, language, visuospatial ability, and perception. Other prominent features include psychomotor disturbance, sleep-cycle derangement, and emotional lability.

The pathogenesis of delirium is not clearly delineated but may relate to cholinergic deficiency and dopaminergic excess.

THE FIRST STEPS: NONPHARMACOLOGIC MANAGEMENT

Inouye[3] outlined a general 3-part approach to managing delirium:

Identify and address predisposing factors. All patients found to have an acute change in mental status should be evaluated for the underlying cause, with special attention to the most common causes, ie, infection, metabolic derangement, and substance intoxication and withdrawal. A thorough medication reconciliation should also be done to identify medications with psychoactive or anticholinergic effects.

Provide supportive care, eg, addressing volume and nutritional status, mobilizing the patient early, and giving prophylaxis against deep venous thrombosis.

Manage symptoms. Behavioral strategies should be instituted in every delirious patient and should include frequent reorientation, use of observers, encouragement of family involvement, avoidance of physical restraints and Foley catheters, use of vision and hearing aids, and normalizing the sleep-wake cycle.

ANTIPSYCHOTICS: ARE THEY SAFE AND EFFECTIVE?

The US Food and Drug Administration (FDA) has not approved any medications for delirium. However, multiple consensus statements, including those by the American Psychiatric Association,[6] the Canadian Coalition for Seniors' Mental Health,[7] and the UK National Institute for Health and Care Excellence,[8] advocate for psychopharmacologic management of delirium symptoms in the following situations:

- The patient is in significant distress from his or her symptoms
- The patient poses a safety risk to self or others
- The patient is impeding essential aspects of his or her medical care.

Guidelines from these organizations recommend antipsychotic medications as the first-line drugs for managing delirium symptoms not caused by substance withdrawal. Nevertheless, the use of antipsychotics in the management of delirium remains controversial. While a number of studies suggest these drugs are beneficial,[9–11] others do not.[12] These consensus panels advocate for the *judicious* use of antipsychotics, limited to the specific situations outlined above.

The use of antipsychotics in elderly and medically complex patients poses risks. One of the most significant safety concerns is increased risk of death due to adverse cardiac events caused by prolongation of the QT interval.

Antipsychotics, QT prolongation, and torsades de pointes

The FDA recommends cardiac monitoring for all patients receiving intravenous haloperidol

Most antipsychotics have the potential to prolong the time of ventricular depolarization and repolarization and the QT interval to some extent, which can lead to torsades de pointes.[13] Other risk factors for prolonged QT interval and torsades de pointes include:

- Long QT syndrome (a genetic arrhythmia)
- Female sex
- Old age
- Electrolyte abnormalities (hypokalemia, hypocalcemia, hypomagnesemia)
- Preexisting heart conditions such as bradycardia, left ventricular dysfunction, heart failure, mitral valve prolapse, and previous myocardial infarction
- Medical conditions that cause electrolyte derangements
- Medications, including antiarrhythmics, antibiotics (macrolides, quinolones), antifungals, antimalarials, antiemetics, some opioids (methadone), and most antipsychotics.

Haloperidol. Postmarketing analysis in 2007 found 73 cases of haloperidol-related

torsades de pointes. However, many of these were confounded by other QT-prolonging medications and medical conditions.[14]

The QT-prolonging effect of haloperidol administered orally or intramuscularly is actually quite small. The equivalent oral dose of 15 mg of haloperidol (assuming 50% bioavailability) given orally or intramuscularly increases the corrected QT interval (QTc) by only 7 to 8 milliseconds. But intravenous haloperidol can cause much more significant QT prolongation: 8 of the 11 reported cases of fatal torsades de pointes occurred when haloperidol was given intravenously.[14] Therefore, the FDA recommends cardiac monitoring for all patients receiving intravenous haloperidol.

Oral olanzapine, risperidone, and quetiapine prolong the QT interval approximately as much as oral haloperidol.

Aripiprazole has not been associated with significant QT prolongation.[13]

Atypical antipsychotics and stroke

The FDA has issued multiple warnings for prescribing antipsychotic medications in the elderly. In 2003, it warned prescribers of increased cerebrovascular adverse events, including stroke, in elderly patients with dementia who were treated with an atypical antipsychotic (risperidone, olanzapine, or aripiprazole) vs placebo.[15]

Quetiapine is the agent of choice in patients with Parkinson disease

Atypical antipsychotics and risk of death

In 2005, the FDA issued a black-box warning about increased all-cause mortality risk in patients with dementia treated with atypical antipsychotics for behavioral disturbance (relative risk 1.6–1.7).[16]

This warning was likely based on a meta-analysis by Schneider et al[17] of trials in which patients with dementia were randomized to receive either an atypical antipsychotic or placebo. The death rate was 3.5% in patients treated with an atypical antipsychotic vs 2.3% in patients treated with placebo, indicating a number needed to harm of 100. The most common causes of death were cardiovascular disease and pneumonia. However, the trials in this meta-analysis included only patients who were prescribed atypical antipsychotics for ongoing management of behavioral disturbances due to dementia in either the outpatient or nursing home setting. None of the trials looked at patients who were prescribed atypical antipsychotics for a limited time in a closely monitored inpatient setting.

Effectiveness of antipsychotics

While several studies since the FDA black-box warning have shown that antipsychotics are safe, the efficacy of these drugs in delirium management remains controversial.

In a 2016 meta-analysis, Kishi et al[18] found that antipsychotics were superior to placebo in terms of response rate (defined as improvement of delirium severity rating scores), with a number needed to treat of 2.

In contrast, a meta-analysis by Neufeld et al[12] found that antipsychotic use was not associated with a change in delirium duration, severity, or length of stay in the hospital or intensive care unit. However, the studies in this meta-analysis varied widely in age range, study design, drug comparison, and treatment strategy (with drugs given as both prophylaxis and treatment). Thus, the results are difficult to interpret.

Kishi et al[18] found no difference in the incidence of death, extrapyramidal symptoms, akathisia, or QT prolongation between patients treated with antipsychotic drugs vs placebo.

In a prospective observational study, Hatta et al[19] followed 2,453 inpatients who became delirious. Only 22 (0.9%) experienced adverse events attributable to antipsychotic use, the most common being aspiration pneumonia (0.7%), followed by cardiovascular events (0.2%). Notably, no patient died of antipsychotic-related events. In this study, the antipsychotic was stopped as soon as the delirium symptoms resolved, in most cases in 3 to 7 days.

Taken together, these studies indicate that despite the risk of QT prolongation with antipsychotic use and increased rates of morbidity with antipsychotic use in dementia, time-limited management of delirium with antipsychotics is effective[9–11] and safe.

SELECTING AND USING ANTIPSYCHOTICS TO TREAT DELIRIUM

Identifying a single preferred agent is difficult, since we lack enough evidence from randomized controlled trials that directly compared the various antipsychotics used in delirium management.

TABLE 1

Antipsychotic agents

Agent	Haloperidol	Olanzapine	Quetiapine	Risperidone	Aripiprazole
Dosage forms	Oral tablets, solution Intramuscular and intravenous solutions	Oral tablets, disintegrating tablets Intramuscular solution	Oral tablets, solution	Oral tablets, disintegrating tablets, solution	Oral tablets, solution, distintegrating tablets Intramuscular solution
Starting dose	0.5–1 mg twice a day	2.5–5 mg twice a day	12.5–25 mg twice a day	0.5 mg twice a day	1 mg twice a day
Half-life (hours)	12–38	21–54	6	20	75
Clearance	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic
Common adverse effects	Akathisia Dystonia Parkinsonism	Akathisia Parkinsonism	Agitation	Parkinsonism	Akathisia Agitation
Effects on corrected QT interval	Oral, intramuscular: Mild Intravenous: Moderate	Mild	Mild	Mild	None
Orthostatic hypotension	Mild	Moderate	Severe	Severe	Moderate
Anticholinergic effects [a]	Mild	Severe	Moderate	Mild	Mild
Sedation	Mild	Moderate	Severe	Moderate	Moderate
Drug-drug interactions (CYP450 activity)	Substrate of: CYP1A2 (minor) CYP2D6 (major) CYP3A4 (major) Inhibits CYP2D6 (moderate)	Substrate of: CYP1A2 (major) CYP2D6 (minor)	Substrate of: CYP2D6 (minor) CYP3A4 (major)	Substrate of: CYP2D6 (major) CYP3A4 (minor)	Substrate of: CYP2D6 (major) CYP3A4 (major)
Special considerations	Minimal effect on vital signs May worsen stiffness and motor symptoms in Parkinson disease	Comes in dissolvable form Helpful for cancer-related nausea Do not combine with parenteral benzodiazepines due to risk of respiratory depression May worsen control of diabetes	Consider in Parkinson disease	Comes in dissolvable form	May be useful for hypoactive delirium No known effect on QTc

[a] Dry mouth, constipation, urinary retention.

Based on information from references 23–25.

Both typical and atypical antipsychotics are used in clinical practice to manage delirium. The typical antipsychotic most often used is haloperidol, while the most commonly used atypical antipsychotics for delirium include olanzapine, quetiapine, risperidone, and (more recently) aripiprazole.

The American Psychiatric Association guidelines[6] suggest using haloperidol because it is the antipsychotic that has been most studied for delirium,[20] and we have decades of experience with its use. Despite this, recent prospective studies have suggested that the atypical antipsychotics may be better because they have a faster onset of action and lower incidence of extrapyramidal symptoms.[18,21]

Because we lack enough head-to-head trials comparing the efficacy of the 5 most commonly used antipsychotics for the management of delirium, and because the prospective trials that do exist show equal efficacy across the antipsychotics studied,[22] we suggest considering the unique pharmacologic properties of each drug within the patient's clinical context when selecting which antipsychotic to use.

Upon discharge, reconcile the medications and discontinue antipsychotics once delirium has resolved

Table 1[23–25] summarizes some key characteristics of the 5 most commonly used antipsychotics.

Haloperidol

Haloperidol, a typical antipsychotic, is a potent antagonist of the dopamine D2 receptor.

Haloperidol has the advantage of having the strongest evidence base for use in delirium. In addition, it is available in oral, intravenous, and intramuscular dosage forms, and it has minimal effects on vital signs, negligible anticholinergic activity, and minimal interactions with other medications.[21]

Intravenous haloperidol poses a significant risk of QT prolongation and so should be used judiciously in patients with preexisting cardiac conditions or other risk factors for QT prolongation as outlined above, and with careful cardiac monitoring. Parenteral haloperidol is approximately twice as potent as oral haloperidol.

Some evidence suggests a higher risk of acute dystonia and other extrapyramidal symptoms with haloperidol than with the atypical antipsychotics.[21,26] In contrast, a 2013 prospective study showed that low doses of haloperidol (< 3.5 mg/day) did not result in a greater frequency of extrapyramidal symptoms.[22] Nevertheless, if a patient has a history of extrapyramidal symptoms, haloperidol should likely be avoided in favor of an atypical antipsychotic.

Atypical antipsychotics

Olanzapine, quetiapine, and risperidone are atypical antipsychotics that, like haloperidol, antagonize the dopamine D2 receptor, but also have antagonist action at serotonin, histamine, and alpha-2 receptors. This multireceptor antagonism reduces the risk of extrapyramidal symptoms but increases the risk of orthostatic hypotension.

Quetiapine, in particular, imposes an unacceptably high risk of orthostatic hypotension and so is not recommended for use in delirium in the emergency department.[27] Additionally, quetiapine is anticholinergic, raising concerns about constipation and urinary retention.

Although the association between fall risk and antipsychotic use remains controversial,[28,29] a study found that olanzapine conferred a lower fall risk than quetiapine and risperidone.[30]

Of these drugs, only olanzapine is available in an intramuscular dosage form. Both risperidone and olanzapine are available in dissolvable tablets; however, they are not sublingually absorbed.

Randomized controlled trials have shown that olanzapine is effective in managing cancer-related nausea, and therefore it may be useful in managing delirium in oncology patients.[31,32]

Patients with Parkinson disease are exquisitely sensitive to the antidopaminergic effects of antipsychotics but are also vulnerable to delirium, so they present a unique treatment challenge. The agent of choice in patients with Parkinson disease is quetiapine, as multiple trials have shown it has no effect on the motor symptoms of Parkinson disease (reviewed by Desmarais et al in a systematic meta-analysis[33]).

Aripiprazole is increasingly used to manage delirium. Its mechanism of action differs from that of the other atypical antipsychotics, as it is a partial dopamine agonist. It is avail-

able in oral, orally dissolvable, and intramuscular forms. It appears to be slightly less effective than the other atypical antipsychotics,[34] but it may be useful for hypoactive delirium as it is less sedating than the other agents.[35] Because its effect on the QT interval is negligible, it may also be favored in patients who have a high baseline QTc or other predisposing factors for torsades de pointes.

BALANCING THE RISKS

Antipsychotic drugs have been shown to be effective and generally safe. Antipsychotics do prolong the QT interval. However, other than with intravenous administration of haloperidol, the absolute effect is minimal. Although large meta-analyses have shown a higher rate of all-cause mortality in elderly outpatients with dementia who are prescribed atypical antipsychotics, an increase in death rates has not been borne out by prospective studies focusing on hospitalized patients who receive low doses of antipsychotics for a limited time.

There are no head-to-head randomized controlled trials comparing the efficacy of all of the 5 most commonly used antipsychotics. Therefore, we suggest considering the unique psychopharmacologic properties of each agent within the patient's clinical setting, specifically taking into account the risk of cardiac arrhythmia, risk of orthostasis and falls, history of extrapyramidal symptoms, other comorbidities such as Parkinson disease and cancer, and the desired route of administration.

At the time the patient is discharged, we recommend a careful medication reconciliation and discontinuation of the antipsychotic drug once delirium has resolved. Studies show that at least 26% of antipsychotics initiated in the hospital are continued after discharge.[36,37]

Current delirium consensus statements recommend limiting the use of antipsychotics to target patient distress, impediment of care, or safety, because of the putative risks of antipsychotic use in the elderly. However, a growing body of evidence shows that low-dose, time-limited antipsychotic use is safe and effective in the treatment of delirium. In fact, González et al found that delirium is an independent risk factor for death, and each 48-hour increase in delirium is associated with an increased mortality risk of 11%, suggesting that delay in treating delirium may actually increase the risk of death.[38]

Therefore, we must balance the risks of prescribing antipsychotics in medically vulnerable patients against the increasing burden of evidence supporting the serious risks of morbidity and mortality of delirium, as well as the costs. Much remains to be studied to optimize antipsychotic use in delirium.

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