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Atypical Antipsychotics for the Treatment of ICU Delirium

Neil A. Gilchrist, PharmD, BCPS1,2, Ifeoma Asoh, PharmD1, and Bruce Greenberg, MD, MBA3

Abstract
Delirium is commonly described in critically ill patients as 1 factor contributing to increased length of intensive care unit and hospital stay, secondary complications, and increased mortality. Initial screening tools for delirium in hospitalized patients are generally easy to use; however, many centers have struggled with implementing these tools in a consistent and systematic manner. Haloperidol has traditionally been prescribed as the primary agent of choice for the treatment of delirium in critically ill patients. Clinicians have been challenged to consider alternative agents due to adverse effects such as extrapyramidal symptoms, QTc prolongation, and possible torsades de pointes with haloperidol use. The atypical antipsychotics are attractive alternatives to haloperidol with improved safety profiles but are flawed by limited data to support dosing and efficacy in this patient population. Future studies that provide large, prospective, double-blinded, placebo-controlled data to support the implementation of these agents as standard therapy over haloperidol are needed.

Keywords
delirium, atypical antipsychotics, olanzapine, quetiapine, risperidone

Introduction
Confusion in acutely ill patients has been described since the time of Hippocrates.1 More recently, delirium in the intensive care unit (ICU) has been identified as a major and underappreciated problem. Delirium is an acute confusional state, whose main features are a fluctuating level of consciousness with reduced awareness of the environment, inattention or disorganized thinking, and abnormal memory.2 As diagnosed by the Confusion Assessment Method for the ICU (CAM-ICU), delirium occurs in about 50% (22%-87%) of the patients admitted to ICU3-6; however, it is unrecognized in the majority of these patients.7 Delirium is associated with increased ICU and hospital length of stay, mortality, placement in skilled nursing facilities, and with higher health care expenditures.4,8-11 Cognitive dysfunction associated with ICU care can persist for months or years even in the absence of preexisting dementia, and ICU delirium may be associated with a dementia-like illness.11 Preexisting dementia is a common risk factor for ICU delirium and delirium occurring in this setting may worsen the prognosis of the dementia.12

The majority of patients with ICU delirium have a hypoactive inattentive delirium rather than the hyperactive type classically seen in hospitalized elderly patients at night.13 The diagnosis therefore relies on a high index of suspicion and the use of a validated diagnostic tool. The most commonly used tool is the CAM-ICU though other instruments exist and have also been validated.14 The CAM-ICU is a simple bedside assessment tool that assists nurses and physicians to diagnose delirium using a stepwise approach. The user of this tool assesses for the presence of abnormal or fluctuating mental status such as variable scores on an ICU sedation scale, inattention manifested by inability to attend to a simple letter or picture recall test, and either disorganized thinking or altered level of consciousness evidenced by incorrect answers to simple questions or inability to follow simple commands.3 Use of the CAM-ICU has increased the identification of ICU delirium, though inclusion of this test has not to our knowledge been associated with improved patient outcomes.

There is only limited data available to guide prevention and treatment of ICU delirium. Detection and management in patients requiring sedation and analgesia for mechanical

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ventilation is especially difficult and benzodiazepine use is common in this patient population. While many risk factors have been identified, few of these are readily modifiable.13 A complex multicomponent intervention has been shown to decrease the frequency and duration of delirium in hospitalized older patients,15 but this has not been repeated in the patients admitted to ICU. This protocol included care guided by multiple geriatric specialists and involved reorienting communication, cognitive stimulation 3 times daily, sleep enhancement, early mobilization, regular encouragement, and visual and auditory assist devices. The studies of alternatives to benzodiazepines, which are a major modifiable risk factor for delirium, have shown cautiously promising results. A 2-center study of 106 mechanically ventilated patients found that the use of dexmedetomidine decreased the incidence of coma and delirium combined in the study patients.16 A larger, multinational study involving 68 hospitals and 375 patients found a 23% absolute reduction in the prevalence of delirium.17 However, widespread use of this agent has been limited due to cardiovascular side effects, cost, and Food and Drug Administration (FDA) approval for only 24 hours of use.

Once delirium is established, there is a dearth of evidence to guide treatment. The Society of Critical Care Medicine guideline recommends haloperidol for the treatment of delirium as a grade C recommendation, which results from limited published data linking positive outcomes to haloperidol therapy.17 Typical antipsychotics such as haloperidol have significant side effects, including anticholinergic effects, QTc prolongation, and extrapyramidal symptoms. These side effects, particularly the risk of QTc prolongation, often preclude use in the patients admitted to ICU. Newer antipsychotics agents tend to have fewer adverse effects and thus offer a promising option for the treatment of ICU delirium. The purpose of this article is to review the atypical antipsychotic agents, their pharmacology, and the available data addressing their use in the treatment of ICU delirium.

**Pharmacology**

Haloperidol, a first-generation antipsychotic, was originally synthesized at Janssen Laboratories in Belgium in 1958 by Paul A. Janssen. This compound showed significant pharmacologic potential by exhibiting antipsychotic activity 50 times more potent than chlorpromazine, the first antipsychotic agent introduced in 1950.18 Over 5 decades later, haloperidol continues to have a significant role in the treatment of psychiatric diseases. Practice guidelines for the treatment of delirium recommend haloperidol as first-line therapy for acute cases.19 With the introduction of the atypical antipsychotics (Table 1), prescribers now have available agents of similar efficacy to haloperidol with reduced risk of adverse side effects, including extrapyramidal symptoms and prolongation of the QTc interval.

The term atypical antipsychotic is not clearly defined but has been used to describe the agents that treat both positive and negative symptoms of schizophrenia. In addition, they produce only a transient elevation in prolactin levels, antagonize the serotonin receptors 5-HT2a and 5-HT2c, block mesolimbic dopamine (DA) receptors over the nigrostriatal neurons, and are efficacious in treatment-resistant schizophrenia.20 The atypical antipsychotic agents include clozapine, olanzapine, quetiapine, risperidone, aripiprazole, ziprasidone, and more recently paliperidone. These agents display varying degrees of dopaminergic-blocking properties at the D2 receptor.21

Clozapine, the first atypical antipsychotic, demonstrated superior efficacy in the management of treatment-resistant schizophrenia;22 however, cases of fatal agranulocytosis are a limiting factor in utilizing this medication in the treatment of ICU delirium.23 As a result, clozapine is not well-studied in the management of ICU delirium. Similarly, paliperidone, the latest atypical antipsychotic is yet to be evaluated in this setting. Therefore, the discussion of atypical antipsychotics in this article will be limited to olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone.

Although atypical antipsychotics share similar mechanisms of action, their pharmacologic activities at neuroreceptors vary widely. The primary sites of activity targeted by these agents include the DA receptors, specifically dopamine (D2) receptors in the mesolimbic system, and serotonin (5-HT) receptors, at the serotonin (5-HT2) receptors throughout the brain.24 Atypical antipsychotics generally have a higher ratio of 5-HT2:D2 blockade than typical antipsychotics. The degree of affinity of atypical antipsychotics for 5HT2 receptors over D2 receptors correlates to their lower propensity to induce EPS.
Among the atypical antipsychotics, ziprasidone displays the highest 5HT2A:D2 ratio and binding affinity to 5HT1D and 5HT1A receptors, displaying antagonist and agonist activity, respectively, and acts as a norepinephrine reuptake inhibitor. These attributes confer decreased risk of inducing EPS and antidepressant and anxiolytic properties; however, the clinical utility of ziprasidone may be limited secondary to the concerns of QTc prolongation and potential development of torsades de pointes. Risperidone is unique in the fact that it displays substantial binding to both D2 and 5-HT2 receptors with similar binding affinities, while the incidence of EPS effects is minimal. This adverse drug effect may be offset based on significant 5-HT2 receptor affinity. Olanzapine, a structural analog of clozapine, displays broad receptor-binding with greater selectivity of D2 receptors located in the mesolimbic regions than other regions (e.g. nigrostriatal). A more comprehensive list of drug-specific receptors is provided in Table 1.

Pharmacokinetics

The pharmacokinetic profiles of atypical antipsychotics have been thoroughly described in previous reports. They are well absorbed in the gastrointestinal tract following oral administration; however, olanzapine undergoes extensive first pass metabolism resulting in approximately 40% of the dose metabolized before reaching systemic circulation. These agents may be administered without regard to food with the exception of quetiapine, which may have increased serum levels with high-fat meals. Pharmacokinetic studies of these agents indicate that oral bioavailabilities range from 60% to 87%. Peak serum concentrations (Cmax) are attained within 1 to 5 hours. These agents are highly plasma protein bound, mainly to albumin and α-1 glycoprotein. Clinically significant drug displacement interactions of atypical antipsychotics with other highly plasma protein-bound drugs are lacking.

Biotransformation of atypical antipsychotics occurs almost exclusively via the hepatic cytochrome P450 (CYP) system. Risperidone undergoes hydroxylation by CYP 2D6 to its active metabolite, 9-hydroxyrisperidone (paliperidone). Genetic polymorphisms of CYP 2D6 create variable responses to risperidone resulting in fairly long elimination half-lives in individuals considered poor metabolizers. The major metabolic pathway of olanzapine involves CYP 1A2 and flavin monooxigenase (FMO), resulting in inactive glucuronidated and desmethylated compounds. Quetiapine is metabolized by CYP 3A4 into several metabolites, 2 of which are active but are considered clinically insignificant. The metabolism of ziprasidone is largely independent of the CYP 450 system, with aldehyde oxidase responsible for 66% of its metabolites.

Elimination of atypical antipsychotics occurs via renal and fecal routes. Terminal elimination half-lives (t1/2) are variable and may be prolonged with some metabolites. Adjustment of doses for renal insufficiency is generally not necessary, as listed in Table 1.

Clinical Trials

Prospective Trials in Critically Ill Patients

There are a limited number of prospective clinical trials evaluating the utilization of atypical antipsychotics in the treatment of delirium of critically ill patients. This section summarizes the clinical trials evaluating atypical antipsychotics in the treatment of delirium in both critically ill and acutely ill patients. The utility of reviewing data for atypical agents in non-ICU patients allows clinicians to extrapolate safety and efficacy data to be used in the patients admitted to ICU.

The most recent trial by Girard et al was a randomized, multicenter, double-blind, placebo-controlled trial involving 101 mechanically ventilated medical and surgical patients admitted to ICU. Patients were randomized to receive either haloperidol, ziprasidone, or placebo every 6 hours for up to 14 days. The primary endpoint was the number of days patients were alive without delirium or coma. Patients included in this study had an abnormal level of consciousness or were receiving sedative or analgesic medications. Baseline characteristics were similar in all 3 groups including median age (51, 54, and 56), median Acute Physiology and Chronic Health Enquiry (APACHE) II scores (26, 26, 26), and median Sequential Organ Failure Assessment (SOFA) scores (11, 10, 11).

Results from this trial showed no difference in the median number of delirium/coma-free days between any of the 3 treatment arms (haloperidol 14.0 days, ziprasidone 15.0 days, placebo 12.5 days, P = .66). Additional results reflected similar findings with no significant difference in median delirium days, ventilator-free days, and length of ICU and hospital stay. To randomize the study drug in a blinded fashion, doses of haloperidol and ziprasidone were administered as oral solutions. Safety data reported from this trial demonstrated no

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**Table 2. Side Effects of Atypical Antipsychotics**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sedation</th>
<th>EPS</th>
<th>NMS</th>
<th>QTc Prolongation</th>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Moderate</td>
<td>Very low</td>
<td>Very low</td>
<td>Very low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Low</td>
<td>Low to moderate</td>
<td>Low to moderate</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Low</td>
<td>Low</td>
<td>Unknown</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Very low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Abbreviations: EPS, extrapyramidal symptoms; NMS, neuroleptic malignant syndrome.

* Seen at doses >6 mg/day.
serious adverse events; however, a minimal number of patients developed symptoms consistent with akathisia (haloperidol 10 patients, ziprasidone 6 patients, and placebo 7 patients, \( P = .60 \)). In all, 10 patients had prolongation of the QTc interval to >500 ms (haloperidol 2 patients, ziprasidone 5 patients, and placebo 3 patients, \( P = .31 \)).

Possible limitations of this study included a small sample size (n = 101), nonstandardized approach to sedation at each study center, and exposure of patients in the ziprasidone and placebo arm to open-label haloperidol therapy. The authors of this study did demonstrate the feasibility of conducting a randomized, placebo-controlled trial in critically ill patients with antipsychotics or placebo. A larger, multicenter, placebo-controlled trial will be needed to accurately determine whether these commonly used agents impact the number of delirium/coma-free days resulting in increased ventilator-free days and reduced length of ICU and hospital days.

A prospective, randomized, double-blind, placebo-controlled study compared the efficacy and safety of scheduled quetiapine to placebo for the treatment of delirium in critically ill patients requiring as-needed haloperidol.\(^{35}\) A total of 36 patients were included in this study and based on their criteria of delirium diagnosed (Intensive Care Delirium Screening Checklist \( \geq 4 \)) by the primary care team, had an order for as-needed haloperidol, and were tolerating enteral nutrition, defined as \( \geq 20 \text{ mL/h} \) for at least 12 hours. Delirium was assessed and documented at baseline and during every nursing shift. Patients randomized to the quetiapine arm received an initial dose of 50 mg every 12 hours. The dose was titrated up daily by increments of 50 mg every 12 hours to a maximum of 200 mg every 12 hours if a patient received at least 1 dose of haloperidol in the previous 24 hours.

The quetiapine group demonstrated a shorter time to the first resolution of delirium (1.0 day vs 4.5 days; \( P = .001 \)), a reduced duration of delirium (36 vs 120 hours; \( P = .006 \)), and less agitation (Sedation-Agitation Scale score \( \geq 5 \)) (6 vs. 36 hours; \( P = .02 \)). Quetiapine-treated patients were also more likely to be discharged home or to rehabilitation versus being transferred to a chronic care facility or dying (89\% vs 56%; \( P = .06 \)). Reported mortality and ICU length of stay were similar between groups. Quetiapine was well tolerated with this rapid escalating regimen. The most common adverse effect observed in quetiapine-treated patients was somnolence and 1 episode of hypotension. There was no statistical difference between quetiapine and placebo for incidence of QTc prolongation and no reports of extrapyramidal symptoms.

A prospective, single-center, randomized trial compared the treatment of delirium in a critical care setting with olanzapine vs haloperidol in 73 medical and surgical patients admitted to ICU.\(^{36}\) All patients admitted were screened for delirium utilizing the ICU Delirium Screening Checklist (ICU-DSC). Patients with an ICU-DSC score of \( \geq 4 \) or with clinical symptoms of delirium received confirmatory diagnosis of delirium using DSM-IV criteria. Initial dosing of olanzapine began at 5 mg daily or haloperidol 2.5 to 5 mg every 8 hours given either orally or via enteral tube.

Results demonstrated a similar decrease in overall delirium indices for both the olanzapine and the haloperidol groups. Additionally, treatment with olanzapine or haloperidol resulted in a decrease of the mean daily dose of benzodiazepines from day 1 to day 5. Safety data in this trial reported no extrapyramidal manifestations with olanzapine therapy while 6 patients in the haloperidol group experienced such symptoms.

Limitations of this study include the use of intravenous haloperidol; however, both groups received similar quantities on day 1 of therapy and rarely required rescue haloperidol in the following 4 days of inclusion. The method of distribution of patients relied upon odd/even day randomization which in the end resulted with an n of 48 in the haloperidol arm and 28 in the olanzapine arm. Additionally, the trial did not blind the treating physicians and nurses to the assigned drug.

A 4th prospective, randomized, double-blind trial compared risperidone and haloperidol in the treatment of delirium in 24 patients from either a medical ward, oncology ward, or ICU.\(^{37}\) The diagnosis of delirium was conducted using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (Third Edition, Revised [DSM-III-R]; SCID). The initial starting dose of haloperidol or risperidone was 0.75 or 0.5 mg by mouth twice daily, respectively, and titrated depending on the symptoms of delirium during the 7-day study period.

The results included no significant difference in mean Delirium Rating Scale scores between the haloperidol and the risperidone groups (21.83 vs 23.50, \( P = .35 \)) or mean Memorial Delirium Assessment Scale scores between groups at day 7. The average time to respond to therapy was 4.22 days in the haloperidol group and 4.17 days in the risperidone group (\( P = .95 \)). In addition, the number of patients who responded on the 3rd day were higher in the haloperidol group (58.4\%) compared to the risperidone group (33.3\%, \( P \) value not reported).

Limitations of this study include a small sample size, possible under dosing of antipsychotics due to a deficiency in data to support any particular dosing regimen, and lack of formal evaluation and reporting process for adverse drug effects. The study population was mixed and the authors did not report how many patients developed delirium while in the ICU. The doses reported are also much lower than the usual doses prescribed in critically ill patients, which may lead to a higher risk of complications if acute delirium and agitation are not controlled effectively.

**Clinical Trials in Acutely Ill Patients**

The role of atypical antipsychotics in the treatment of delirium in noncritically ill patients has been reviewed extensively by Periottianni et al.\(^{38}\) The first report of utilizing atypical agents included risperidone for the treatment of delirium in a group of 11 patients.\(^{39}\) Although this study did not have a comparator group or a standardized scoring system of delirium, this led the same authors to a later trial comparing olanzapine to haloperidol for delirium.\(^{40}\) The results of this trial demonstrated significant improvement with both treatment groups; the olanzapine group reported no side effects, while 5 patients...
in the haloperidol group had either extrapyramidal symptoms or excessive sedation. The conclusion that olanzapine, as well as other atypical agents, may be similar in efficacy to haloperidol with minimal to no adverse effects intrigued many clinicians to look further.

Since the first trial with risperidone, there have been well over a dozen trials evaluating the efficacy of atypical agents for delirium. The majority of these studies are limited due to their small sample size, open label or retrospective design, and single-center participation. Despite these limitations, these studies provide useful information in dosing strategies (Table 1) that did not result in significant adverse effects when used alone, compared to haloperidol, or when combined with open-label haloperidol therapy in noncritically ill patients.

**Adverse Effects**

The most commonly reported adverse effects in clinical trials using antipsychotics for ICU delirium include QTc prolongation, EPS, and sedation. These adverse effects have been reported with both atypical agents and haloperidol therapy. The lower incidence of EPS observed with atypical agents is most likely associated with the effect on 5-HT receptors, as previously discussed in this article. There is limited information that the risk of EPS may differ between routes of administration of haloperidol. An abstract evaluating this risk retrospectively in 238 participants receiving haloperidol found IV therapy had a lower incidence compared to PO treatment (7.2% vs 22.6%; no P value reported). Comparison of IV vs PO therapy and risk of adverse effects has not been thoroughly reported with atypical antipsychotics to date.

Aside from the pharmacologic targets of these drugs, adverse effects are seen secondary to activity at D2 receptors in the striatum and tuberohypophysial DA tracts, adrenergic receptors, muscarinic receptors, and histaminergic receptors. Atypical antipsychotics are associated with a decreased capacity to induce neurological disorders compared to conventional agents but result in a higher incidence of metabolic side effects. The side effects which may be observed in the short-term administration may include QTc prolongation, movement disorders, sedation, hyperglycemia, seizures, and neuroleptic malignant syndrome (NMS). Adverse effects seen with prolonged therapy may include weight gain, the development of diabetes mellitus, and elevated prolactin levels (Table 2).

Electrocardiogram (ECG) abnormalities, representative of QTc prolongation, have been associated with antipsychotic therapy. Reports of QTc prolongation leading to torsades de pointes with resulting cardiac death has led to some antipsychotics to fall out of favor. Among the atypical agents, ziprasidone has been shown to have the most potential to prolong the QTc interval at doses used in the clinical trials. A prospective, open-label trial investigated the cardiovascular effects of ziprasidone and other antipsychotics in 164 patients. Treatment regimens included ziprasidone 160 mg/day, quetiapine 750 mg/day, olanzapine 20 mg/day, risperidone 6 to 16 mg/day, haloperidol 15 mg/day, and thioridazine 300 mg/day. QTc prolongation was greatest in the thioridazine group followed in descending order by ziprasidone, haloperidol, quetiapine, risperidone, and olanzapine. QTc prolongation >75 ms occurred in the ziprasidone arm; however, no cases of torsades de pointes were reported. The risk of sudden cardiac death is highest in patients with underlying cardiac disease already taking medications known to prolong QTc.

All antipsychotics have the potential to induce extrapyramidal symptoms including akathisia, dyskinesia, and pseudo-parkinsonism. It is hypothesized that the newer antipsychotics are distinguished by their decreased propensity to induce movement disorders secondary to their specificity for limbic D2 receptors and high 5HT2A receptor binding. This dose-dependent relationship has been identified with risperidone and quetiapine in doses >6 and 20 mg/day, respectively. The risk of EPS appears to be minimal with a rapidly escalating regimen of quetiapine up to 200 mg twice daily.

Due to their antagonism at the H1 receptor, sedation is a common side effect of these agents. Olanzapine displays the most potent H1 receptor antagonist correlating to its high incidence of sedation with up to 30% of patients reporting such symptoms in clinical trials. Quetiapine and risperidone are less sedating followed by ziprasidone and aripiprazole. This property may be beneficial in the patients admitted to ICU requiring large amounts of sedating benzodiazepines as a mechanism to utilize alternative pharmacologic targets.

The major metabolic effects of atypical antipsychotics include weight gain and development of diabetes mellitus. These are effects that would generally be out of the context of the ICU population. The underlying mechanism of hyperglycemia may be more relevant with the data supporting glycemic control in critically ill patients. These agents are thought to induce hyperglycemia by affecting the secretion and action of hormones involved in glucose and lipid metabolism. To date, there are no randomized trials evaluating the effect of atypical antipsychotics on glycemic control in the patients admitted to ICU. This information may prove to be useful in determining the optimal agents to use in this class.

Less common but potentially serious adverse effects include seizures and NMS. Neither of these adverse effects was observed during the clinical trials discussed in this article; however, each has been reported in a number of published case reports. Antipsychotics as a class may increase the risk of seizures with an incidence of less than 2%. Of the atypical agents, clozapine appears to be the biggest offender in a concentration-dependent manner. Doses greater than 600 mg have been reported to have a high incidence (4.4%) of seizures compared to lower doses (300-600 mg/day 2.7%; <300 mg/day 1.0%). Neuroleptic malignant syndrome, a potentially fatal syndrome, rarely occurs with atypical antipsychotic with an incidence of less than 1% for all antipsychotics. Several cases of olanzapine, risperidone, and quetiapine-induced NMS have been reported. However,
NMS was not observed in safety studies of atypical antipsychotics in the management of critically ill delirious patients previously described in this article.

**Drug Interactions**

The atypical antipsychotics generally do not affect the metabolism of other drugs, as do the typical antipsychotics. Atypical antipsychotics are neither inducers nor inhibitors of the CYP isoenzymes, a major enzymatic family responsible for the metabolism of many pharmacologic agents including antipsychotics. Drug-drug interactions involving atypical antipsychotics generally result from the effect of other drugs on their metabolism. Drugs such as ketoconazole, a potent CYP 3A4 inhibitor, have led to the decreased metabolism of ziprasidone, resulting in increased serum concentrations and prolonged QTc intervals. An extensive review of antipsychotic drug-drug interactions has been previously reported including coadministration of antipsychotics with antidepressants, anxiolytics, anticholinergics, and individual enzyme-altering medications. A practical approach to minimize toxicity from drug-drug interactions would be using clinical decision support software to detect the interactions, minimize the exposure time and adjust the dose(s) of medications that interact, and consider alternative therapies which do not affect metabolizing enzyme activity.

Clinicians may observe adverse effects of drugs acting at the same pharmacologic receptors. Previous discussion in the article described the propensity of this class of drugs to prolong the QTc interval; however, in a much less-significant amount than typical antipsychotics, with the exception of ziprasidone. Table 3 lists the commonly prescribed medications in the ICU setting which are associated with QTc prolongation. It is the multiple combinations of these agents in critically ill patients that create an increased risk for this adverse effect. Prescribers should consider the multiple receptors that atypical antipsychotics affect to avoid additive toxicity.

**Conclusion**

Delirium is a common clinical finding in critically ill patients, which requires accurate clinical assessment and appropriate pharmacologic therapy to reduce prolonged ICU and hospital stay. Antipsychotic medications should be considered as part of the pharmacologic regimen for the treatment of ICU-associated delirium. Limited data suggest that atypical antipsychotics are more effective than placebo in decreasing the duration of delirium and degree of agitation that patients may experience. In addition, this therapy may lead to increased discharges home or to a rehabilitation facility. Comparison to haloperidol therapy has shown similar efficacy but with reduced incidence of adverse effects. Clinicians should consider atypical antipsychotics as safe and effective in the treatment of ICU delirium with short-term therapy. Further studies will be needed to determine the cost-effectiveness of using these agents in place of haloperidol therapy.

**References**


