JPPT | Review

Antipsychotic Use in the Prevention and Treatment of Intensive Care Unit Delirium in Pediatric Patients

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OBJECTIVES To describe the antipsychotics, route of administration, dosage regimen, and outcomes reported to prevent or treat delirium in hospitalized children.

METHODS Medline, Embase, and International Pharmaceutical Abstracts were searched using the keywords "haloperidol," "olanzapine," "quetiapine," "risperidone," "ziprasidone," and "delirium." Articles evaluating the use of these agents to manage delirium in hospitalized children that were published between 1946 and August 2019 were included. Two authors independently screened each article for inclusion. Reports were excluded if they were published abstracts or included fewer than 3 patients in the report.

RESULTS Thirteen reports that included 370 children receiving haloperidol, quetiapine, olanzapine, and/or risperidone for delirium treatment were reviewed. Most children received haloperidol (n = 131) or olanzapine (n = 125). Significant variability in dosing was noted. A total of 23 patients (6.2%) had an adverse drug event, including 13 (56.5%) who experienced dystonia and 3 (13.0%) with a prolonged corrected QT interval. Most reports described improvement in delirium symptoms; however, only 5 reports used a validated screening tool for PICU delirium to evaluate antipsychotic response.

CONCLUSIONS Most reports noted efficacy with antipsychotics, but these reports were limited by sample size and lacked a validated PICU delirium tool. Future research is needed to determine the optimal agent and dosage regimen to treat PICU delirium.

ABBREVIATIONS ADE, adverse drug event; CAPD, Cornell Assessment of Pediatric Delirium; DC, Discontinuation; DRS-R-98, Delirium Rating Scale-Revised-98; ECG, electrocardiogram; EPS, extrapyramidal symptoms; FDA, Food and Drug Administration; ICU, intensive care unit; IM, intramuscular; IQR, interquartile range; IV, intravenous; NMS, neuroleptic malignant syndrome; NPO, nothing by mouth; pCAM-ICU, Pediatric Confusion Assessment Method for the ICU; PICU, pediatric intensive care unit; psCAM-ICU, Preschool Confusion Assessment Method for the ICU; QTc, corrected QT; SOS-PD, Sophia Observation Withdrawal Symptoms-Pediatric Delirium

KEYWORDS children; delirium; haloperidol; intensive care; olanzapine; quetiapine; risperidone

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Introduction

Intensive care unit delirium is a mental disturbance characterized by abrupt onset of decreased awareness and cognition in critically ill patients.[1] In both the adult and pediatric ICU, delirium can be categorized as hypoactive (e.g., decreased responsiveness), hyperactive (e.g., agitation and combativeness), or mixed.[1] In 1 single-center study, investigators reported an overall incidence of delirium to be 17.3% in their PICU, with hypoactive delirium as the most common phenotype (46.4%), followed by mixed (45.2%), and hyperactive being the least common (8.4%).[2] In adults, a high incidence of delirium has been reported in critically ill patients, with up to 80% of mechanically ventilated adults experiencing delirium during their ICU stay.[3] Historically, the prevalence of ICU delirium in pediatric patients has been underreported because of the lack of validated tools that could be used to assess delirium in this population. However, within the last 6 years several tools have been developed and validated including the pediatric Confusion Assessment Method for the ICU (pCAM-ICU) for children older than 5 years, the Preschool Confusion Assessment Method for the ICU (psCAM-ICU) for children ages 6 months to 5 years, and the Cornell Assessment of Pediatric Delirium (CAPD) for children ages 0 to 21 years.[4–6] With the development of these tools, the prevalence of PICU delirium has been reported to occur in between 12% and 65% of children admitted to various ICU settings.[1,7] PICU delirium can contribute to longer duration of mechanical ventilation, increased length of hospital stay, long-term cognitive impairment, morbidity, and mortality.[2]

To date, there are no guidelines in the United States

for the assessment and management of pediatric delirium, and there are limited data for prevention and treatment strategies for pediatric delirium. Although no agents are currently labeled by the FDA for the prevention or treatment of ICU delirium in adult or pediatric patients, antipsychotics are commonly used off-label for prevention and treatment.[3,8] The purpose of this review is to describe the role of antipsychotics for either prevention or treatment of PICU delirium.

Literature Review

Relevant articles were identified using Medline (1946–August 2019), Embase (1988–August 2019), and International Pharmaceutical Abstracts (1970–August 2019), using the terms "haloperidol," "olanzapine," "quetiapine," "risperidone," and "ziprasidone," as well as the additional terms "children" and "delirium." Results were limited to studies in humans, published in the English language. Published abstracts were not included because of a lack of essential details. Thus, the search was limited to published studies, letters to the editor, and case reports.

A 2-step process was conducted. Initial reports were screened by 2 reviewers (A.C. and S.B.), and then all authors were involved in the final selection process. To be included for analysis, the report had to include at least 3 patients younger than 18 years who received at least 1 of the selected antipsychotics for ICU delirium. The second step involved screening the references cited in the included studies to identify additional studies that were not located with the initial search.

Overview of Literature

A total of 42 articles were identified using the indexing search strategy. An additional 9 papers were identified by screening the references list of those 42 articles. All 51 articles focused on delirium treatment, and no reports evaluated delirium prevention. A total of 38 of the 51 articles were excluded because they were review articles or involved case reports of fewer than 3 children. A total of 13 reports involving 370 children were included for analysis.[9–21] Two patients received combination therapy with 2 different agents.[14] Of those that described the study site, most of the reports evaluated agents used for PICU delirium,[9–14,16–18,20] with only 1 report evaluating an antipsychotic in the NICU setting.[19] Two reports evaluated antipsychotics that included patients in the PICU and other locations in the hospital setting.[15,21] Tables 1 through 4 provide an overview of the type of report, dosage regimen, and outcomes reported for each antipsychotic.

Haloperidol. Haloperidol results are given in Table 1. Harrison et al[9] reported their experience with IV haloperidol for the control of severe agitation or delirium in 5 children, ranging from 9 months to 16 years of age, in the PICU. All of the children were mechanically ventilated and received opioids, sedatives, and neuromuscular blockers. Patients received an initial haloperidol dose of 0.025 to 0.1 mg/kg per dose IV every 10 minutes until resolution of agitation was achieved. Most patients required 3 to 4 doses to achieve resolution of agitation, with total loading doses ranging from 0.09 to 0.25 mg/kg. In addition, patients received a mean maintenance dose of 0.07 mg/kg per dose (range, 0.015–0.15 mg/kg per dose) IV every 6 to 8 hours. The authors did not report if the haloperidol was tapered prior to discontinuation, and the duration was only reported in 1 patient who received 3 days of maintenance therapy. It is important to note that assessment of agitation and delirium was not conducted using a validated tool, but rather based on clinical findings. One patient who developed a dystonic reaction during maintenance therapy received a total initial haloperidol dose of 0.1 mg/kg followed by a maintenance dose of 0.025 mg/kg per dose IV every 6 hours. Symptoms resolved within 36 hours of haloperidol discontinuation. No other adverse drug events (ADEs) were noted. This report provides some evidence that haloperidol may alleviate agitation, but resolution of delirium cannot be demonstrated because of the lack of a validated scoring tool.

Ratcliff et al[10] performed a retrospective chart review in 26 children with a mean age of 11.7 ± 3.9 years. Patients were admitted to the PICU with a burn injury and received IV or enteral haloperidol for delirium and agitation. A total of 22 children (84.6%) were mechanically ventilated, and most received opioids, benzodiazepines, and diphenhydramine. Most patients (96.2%) received more than 1 dose of IV haloperidol, and loading doses were not described in the study. The mean dose of haloperidol was 0.057 mg/kg (range, 0.013–0.278 mg/kg). The mean number of doses was 12 ± 30. One patient received haloperidol for up to 22 days. There was no mention of whether the haloperidol was tapered prior to discontinuation. Each patient was assigned a score upon chart review based on the effectiveness of haloperidol using a non-validated scoring tool (0 = no effect, 1 = fair, 2 = good, and 3 = excellent). Minimal relief of agitation and delirium (score 0–1) was noted in 13 children (50%). A total of 6 children (23%) experienced an ADE, including dystonia (n = 4), hyperpyrexia (n = 1), and dystonia and hyperpyrexia (n = 1). For the patients with dystonia, the symptoms resolved with reduction or discontinuation of haloperidol, or initiation of diphenhydramine. Although the authors did not note if the patient with hyperpyrexia had additional symptoms of neuroleptic malignant syndrome (NMS), dantrolene was given. For the child with dystonia and hyperpyrexia, the dystonia was initially managed with diphenhydramine and benztropine; however, this patient subsequently developed hyperpyrexia and died 8 hours later. The authors commented that the hyperpyrexia was associated with haloperidol administration, and on autopsy

Table 1. Experience With Haloperidol for Delirium In Critically Ill Pediatric Patients

Reference (Study Type)	Sample Size	Age, yr	Dose	Duration (Tapering)	Scoring Tool Used	Results
Harrison[9] (case series)	N = 5	12 (0.92–14)*	0.025–0.1 mg/kg/dose IV every 10 min until agitation resolves. Then 0.015–0.15 mg/kg/dose IV every 6–8 hr	3 days in 1 patient (NR)	NR	Most required 3–4 initial doses for control; dystonic reaction in a patient hat resolved after DC
Ratcliff[10] (retrospective)	N = 26	11.7 ± 3.9†	0.057 mg/kg (0.013–0.278 mg/kg) 96.1% received IV haloperidol	Doses 2 ± 30‡ Max duration in 1 pt was 22 days (NR)	Non-validated agitation scale	Good to excellent delirium relief (score of 2–3 on non-validated scale noted in 13 [50%]). Six pts had an ADE: dystonia (n = 4), hyperpyrexia (n = 1), or dystonia and hyperpyrexia (n = 1) that resolved after dose reduction, DC, or anticholinergic.
Schieveld[11] (prospective)	N = 40; haloperidol (n = 28); risperidone (n = 10); no antipsychotic (n = 2)	9.0 (1.8–14.3)* for haloperidol	Planned initial and maintenance doses of IV haloperidol: 0.15–0.25 mg and 0.05–0.5 mg/kg/day, respectively§	NR (NR)	NR, did employ neuropsychiatrist assessment	Delirium categorized in those receiving haloperidol as hyperactive (n = 9; 32.1%), mixed (n = 13; 46.4%), and hypoactive (n = 6; 21.4%). Pts receiving haloperidol for hyperactive delirium responded rapidly. Two pts experienced acute dystonia that responded to an anticholinergic.
Slooff [12] (retrospective)	N = 52	Overall not reported	Medidose received in patients with adverse effects 0.03 mg/kg/day (0.02–0.05 mg/kg/day)¶ Dose received without ADEs: 0.02 mg/kg/day (0.003–0.08 mg/kg/day)¶	NR (NR)	NR	No report on efficacy. Five pts had ADE that included tremor/dystonia/decreased level of consciousness (n = 1), oculogyric crisis/drooling/fever (n = 1), fever/tachycardia/NMS (n = 1), oculogyric crisis/cogwheel rigidity (n = 1), and muscle rigidity (n = 1) that resolved to dose reduction, DC, or anticholinergic.

ADE, adverse drug effect; CAPD, Cornell Assessment of Pediatric Delirium; DC, Discontinuation; DRS-R-98, Delirium Rating Scale-Revised-98; EPS, extrapyramidal symptoms; Max, maximum; NMS, neuroleptic malignant syndrome; NR, not reported; pt, patient; QTc, corrected QT; SOS-PD, Sophia Observation Withdrawal Symptoms-Pediatric Delirium

* Median (IQR).

† Mean ± SD.

‡ Mean (range).

§ Specific dosing details, including dosing frequency, not provided.

¶ Median (range).

Table 1. Experience With Haloperidol for Delirium In Critically Ill Pediatric Patients *(cont.)*

Reference (Study Type)	Sample Size	Age, yr	Dose	Duration (Tapering)	Scoring Tool Used	Results
Slooff [13] (prospective, pharmacokinetic)	N = 13	8.3 (0.4–13.8)¶	Dose received: 0.027 mg/kg/day (0.005–0.085 mg/kg/day)¶	4 days (1–34 days)¶ (NR)	SOS-PD	Delirium resolved in all pts as assessed by the SOS-PD. Five pts developed ADEs despite haloperidol serum concentrations less than therapeutic range. Pts who developed ADEs received a higher dose and longer duration than those who did not have any ADEs. ADEs included EPS (n = 4) and sedation (n=2), which resolved with decreased dose, DC, or anticholinergic.
Kishk[14] (retrospective, matched cohort)	N = 15; haloperidol (n = 6); haloperidol and risperidone (n = 1); quetiapine, risperidone, or combination (n = 8)	0.66 (0.54–2.3)* for haloperidol	Planned urgent dose, every 15–20 min until agitation controlled: <3 yr: 0.025 mg/kg; ≥3 yr: 0.5–1 mg; Planned maintenance dose: 0.05–0.15 mg/kg/day divided every 6–12 hr; Specific dosing details NR.	NR (NR)	CAPD	Delirium resolved in a median of 6 days for haloperidol-treated pts. CAPD scores 24 hr after initiation of haloperidol decreased by a median of 6 points. No ADEs were reported.

ADE, adverse drug effect; CAPD, Cornell Assessment of Pediatric Delirium; DC, Discontinuation; DRS-R-98, Delirium Rating Scale-Revised-98; EPS, extrapyramidal symptoms; Max, maximum; NMS, neuroleptic malignant syndrome; NR, not reported; pt, patient; QTc, corrected QT; SOS-PD, Sophia Observation Withdrawal Symptoms-Pediatric Delirium

* Median (IQR).

† Mean ± SD.

‡ Mean (range).

§ Specific dosing details, including dosing frequency, not provided.

¶ Median (range).

Table 2. Experience With Quetiapine for Delirium in Critically Ill Pediatric Patients

Reference (Study Type)	Sample Size	Age, yr	Dose	Duration (Tapering)	Scoring Tool Used	Results
Turkel[15] (retrospective)	N = 110. Quetiapine (n = 19); remainder received olanzapine or risperidone (n = 91)	10.8 ± 4.5* for quetiapine	Initial dose: 30 mg/day (12.5–100 mg/day)*; Max daily dose 75 mg/day (12.5–300 mg/day)*	35.1 days (1–108 days)* (NR)	DRS-R-98	Change in DRS-R-98 after quetiapine 12.4 ± 5.2*; No ADEs reported.
Traube[16] (case series)	N = 4	Range: 0.67–14	Initial dose range: 0.43–0.7 mg/kg per dose every 8 hr; max dose range: 0.73–2.8 mg/kg per dose every 8 hr	9–20 days (n = 2)	CAPD	Hyperactive delirium symptoms decreased within 24 hr. Decrease in sedative and opioid doses achieved after quetiapine initiation. No reported ADEs.
Traube[17] (case series)	N = 4	Range: 0.58–3	Not provided	NR (n = 1)	CAPD	Delirium symptoms improved in 2 pts within 24 hr. No ADEs reported.
Joyce[18] (retrospective)	N = 50	4.5 (0.17–20)*	0.43 mg/kg per dose every 8 hr (0.13–0.77 mg/kg per dose)†	12 days (4.5–22 days)† (NR)	CAPD	CAPD scores for assessment, but no efficacy data of delirium resolution reported. Three pts (6.0%) had QTc prolongation without torsade de pointes. No EPS or NMS.
Groves[19] (case series)	N = 3	Premature infants, but specific age NR	Initial dose: 0.5 mg/kg per dose every 8 hr	Specific duration not provided, at least 2 wk to 2 mo (n = 1)	CAPD	All 3 had improvement of delirium within 72 hr. Two pts had CAPD score reduction by about 8 points 3–5 days after quetiapine initiation. No ADEs reported.
Kishk[14] (retrospective, matched cohort)	Retrospective, matched cohort, n = 15 (quetiapine, n = 1; quetiapine/risperidone, n = 1; remainder received haloperidol, risperidone, or combination therapy, n = 12)	14 received monotherapy or combination therapy	Planned maintenance dose: 12.5–25 mg every 12 hr. Specific dosing not provided.	NR (NR)	CAPD	Delirium resolved after 3 days in quetiapine monotherapy pt. CAPD scores 24 hr after initiation of quetiapine monotherapy decreased by 13 and 7 points in pts receiving quetiapine or risperidone. No ADEs reported.

ADE, adverse drug event; CAPD, Cornell Assessment of Pediatric Delirium; DRS-R-98, Delirium Rating Scale-Revised-98; EPS, extrapyramidal symptoms; NME, neuroleptic malignant syndrome; pt, patient; QTc, corrected QT; SOS-PD, Sophia Observation Withdrawal Symptoms-Pediatric Delirium

* Mean ± SD.

† Median (IQR).

Table 3. Summary of Olanzapine Use for Delirium in Critically Ill Pediatric Patients

Reference (Study Type)	Sample Size	Age, yr	Dose	Duration (Taper)	Scoring Tool Used	Results
Turkel[15] (retrospective)	N = 110; olanzapine, (n = 78); quetiapine or risperidone (n = 32)	10.8 ± 4.9* for olanzapine group	Initial daily dose received: 4 mg/day (0.625–30 mg/day)† Maximum daily dose: 10 mg/day (1.25–60 mg/day)†	26.5 days (1–132 days)† (NR)	DRS-R-98	Mean change in DRS-R-98 after olanzapine administered was 15.7 ± 5.6. One patient (1.3%) had ADE of dystonia reported that resolved with reduction in dose.
Sassano-Higgins[20] (retrospective)	N = 59 (olanzapine, n = 31; and control, n = 28)	9.2 ± 6.2* yr for olanzapine	Initial planned dose for infants was 0.625 mg once to twice daily for infants, 1.25 mg once to twice daily for toddlers, and 2.5–5 mg once to twice daily for older, larger, extremely agitated children. Specific dosing details received not provided.	NR (NR)	DRS-R-98	Significant delirium symptom improvement as noted by the DRS-R-98 in the olanzapine versus control group, after controlling for initial delirium severity. No ADEs were reported.
Turkel[21] (retrospective)	N = 19 (olanzapine, n = 16 and risperidone, n = 3)	1.6 yr (0.57–2.8 yr)‡	Initial daily dose: 1.25 mg/day (0.5–20)‡ Maximum daily dose: 3.75 mg/day (1.25–35)‡	23 days (1–151 days)‡ (NR)	DRS-R-98	All children younger than 3 yr and had symptom improvement as noted by DRS-R-98. Significant mean decrease of 10.6 ± 2.4 in DRS-R-98 between pre vs post olanzapine or risperidone. No ADEs reported.

ADE, Adverse Drug Effect; DRS-R-98=Delirium Rating Scale-Revised-98; NR, not reported

* Mean ± SD

† Mean (range)

‡ Median (range)

the cause of death was attributed to renal and respiratory failure. Patients with ADEs had a longer duration of haloperidol therapy (9.7 ± 4.6 vs 3.7 ± 5.6 days, p = 0.03) and received a greater number of IV doses (14 ± 9 vs 5 ± 5, p = 0.01), but had a non-significantly higher dose (0.08 ± 0.06 vs 0.05 ± 0.03 mg/kg), than patients with no ADEs. This report included only burn patients, and as such, applications to other PICU populations are limited. The use of a non-validated scoring tool made it difficult to objectively assess efficacy. The authors concluded that IV haloperidol should be used sparingly.

Schieveld et al[11] conducted a retrospective study of children with delirium who received haloperidol or risperidone. The authors identified 40 patients who experienced delirium based on clinical assessment and evaluated the use of antipsychotics in 38 patients. A total of 28 patients (70%) were initiated on IV haloperidol, and 1 patient was later transitioned to enteral risperidone. The median age of those initiated on haloperidol was 9.0 years. The authors did not specify an initial and maintenance dose in milligrams per kilograms per dose, whether the haloperidol was tapered prior to discontinuation, or if a delirium scoring tool was used. A total of 9 patients (32.1%) were noted to have hyperactive delirium, with 6 (21.4%) developing hypoactive and 13 (46.4%) developing mixed delirium. Many patients with hyperactive delirium responded to the initial dose of haloperidol, but responses varied from hours to days depending on the type of delirium experienced. It was difficult to determine from the report if this delayed response was due to the type of delirium (e.g., mixed or hypoactive), the use of haloperidol versus risperidone, or the dosing used. A total of 2 patients (7.1%) receiving haloperidol developed dystonia and were treated with an anticholinergic. Based on this report, patients receiving haloperidol with hyperactive

Table 4. Summary of Risperidone for Delirium in Critically Ill Pediatric Patient

Reference (Study Type)	Sample Size	Age, yrs	Dose	Duration (Taper)	Scoring Tool Used	Results
Schieveld[11] (prospective)	N = 40; risperidone (n = 10); haloperidol (n = 28); or no antipsychotic (n = 2)	7 (2.8–9)* for risperidone group	Planned initial dose: 0.1–0.2 mg/day. Planned maintenance dose: range 0.2–2 mg/day. Specific dosing details including dosing frequency not provided	NR (NR)	NR	Delirium categorized in those receiving risperidone as hyperactive (n = 9; 32.1%), mixed (n = 13; 46.4%), and hypoactive (n = 6; 21.4%). No ADEs reported.
Turkel[15] (retrospective)	N = 110; risperidone (n = 13; remainder received olanzapine or quetiapine (n = 97)	8.6 ± 5.4† for risperidone group	Initial daily dose: 0.6 mg/day (0.25–1 mg/day)‡ Maximum daily dose: 1 mg/day (0.25–2 mg/day)‡	17.5 days (2–54 days)‡ (NR)	DRS-R-98	Change in DRS-R-98 after risperidone administered was 15.3 ± 6.0†. No ADEs reported.
Turkel[21] (retrospective)	N = 19; risperidone (n = 3); olanzapine (n = 16)	1.6 (0.57–2.8)* for risperidone group	Initial daily dose: 0.25 mg/day (0.1–0.25 mg/day)§ Maximum daily dose: 0.25 mg/day (0.1–0.5 mg/day)§	25 days (2–151 days)§ (NR)	DRS-R-98	All children <3 yr had symptom improvement as noted by a significant decrease of 10.6 ± 2.4† in DRS-R-98 between pre vs post risperidone or olanzapine. No ADEs reported.
Kishk[14] (retrospective)	N = 15; risperidone (n = 6); risperidone/quetiapine (n = 1); remainder received haloperidol, quetiapine, or combination therapy (n = 8)	1.6 (1.3–2.7)* for risperidone monotherapy; 7.2 (0.57–14)* for risperidone combination therapy	Planned maintenance dose: <5 yr: 0.1 mg q 12–24 hr; ≥5 yr: 0.2 mg every 12–24 hr. Specific dosing details received not provided.	NR (NR)	CAPD	Delirium resolved in a median of 3.5 days for risperidone monotherapy and 5–12 days for the combination therapy. Patients' CAPD scores decreased 24 hr after initiation by a median of 9 points in those on risperidone monotherapy and by 7–14 points for those given combination therapy. No ADEs were reported.

ADE, adverse drug effect; NR, not reported

* Median (IQR).

† Mean ± SD.

‡ Mean (range).

§ Median (range).

delirium responded quickly. Because of limited details regarding the haloperidol dosage regimen, it is difficult to determine the specific dosage regimen needed to achieve cessation of delirium symptoms.

Slooff et al[12] performed a retrospective chart review to evaluate the frequency and nature of haloperidol-related ADEs in 52 critically ill children with a diagnosis of delirium who received oral or IV haloperidol. The mean age was not reported for all 52 patients, but was only noted for those with ADEs. A total of 5 children (9.6%) experienced an ADE, which included dystonia (n = 4) and suspected NMS (n = 1). Although ECG was assessed for prolongation of the corrected QT (QTc) interval, the authors did not comment on how often this was repeated. There was no mention of loading doses or tapering of haloperidol in this report. There was no significant difference in the median (range) dose of haloperidol received in patients with and without ADEs, 0.03 mg/kg/day (0.02–0.05 mg/kg/day) versus 0.02 mg/kg/day (0.003–0.08 mg/kg/day). In addition, there was no difference in the median (range) age between those with and without an ADE, 6.3 years (3.9–15.0 years) versus 11.7 years (0.25–18.8 years). Although 52% of the study population was female, it is interesting that all 5 patients who experienced an ADE were female. The ADEs occurred within 3 days of haloperidol administration. These ADEs resolved with the following: dose reduction (n = 2), discontinuation (n = 1), or administration of an anticholinergic (n = 2). Similar to other reports, about 10% of children given haloperidol experienced AEDs. This report is limited with its small sample size, retrospective design, and lack of efficacy assessment.

Slooff et al[13] described a haloperidol dose-titration protocol in 13 children with a median age of 8.3 years with delirium. They monitored serum haloperidol concentrations to optimize efficacy and limit ADEs. Patients were assessed for QTc prolongation at baseline and then daily during haloperidol administration. A total of 11 patients received IV haloperidol, 1 patient received oral haloperidol, and 1 patient received both IV and oral formulations. Patients were initiated on a loading dose of 0.05 to 0.25 mg per dose IV or 0.01 to 0.025 mg/kg per dose orally followed by a maintenance dose of 0.01 to 0.05 mg/kg/day IV or variable oral dosing. Doses were adjusted daily depending on clinical response, serum haloperidol concentration (goal: 3–12 mcg/L), and occurrence of an ADE. The median (range) dose of haloperidol was 0.027 mg/kg/day (0.005–0.085 mg/kg/day). Efficacy was determined by improvement in Sophia Observation withdrawal Symptoms-PD (SOS-PD) scores and via psychiatric evaluation, and delirium was considered to be resolved in all cases. A total of 5 children (38.5%) experienced extrapyramidal symptoms (EPS; n = 4; 30.8%) and/or sedation (n = 2; 15.4%). Serum concentrations were less than 2 mcg/L in each of these patients, and the authors noted that there was no correlation between haloperidol serum concentrations and the appearance of ADEs. Although p values were not reported, patients who developed ADEs received a higher median (range) mg/kg/day dose (0.043 [0.005–0.085]) and were treated for a longer duration (6 days [2–34 days] vs 3 days [1–19 days]) than those without ADEs, These ADEs were resolved with dose reduction (n = 3), discontinuation (n = 3), or administration of an anticholinergic (n = 2). Interestingly, delirium did not reoccur following these interventions. There was no mention on whether the haloperidol was tapered prior to discontinuation. The authors concluded that haloperidol can improve delirium; however, there are risks of an ADE. This study's small sample size limited the ability to make comparisons between the 2 groups to determine potential risk factors for ADEs. Additionally, the sample size precluded the authors from determining the statistical significance of a higher dose of haloperidol and longer duration of treatment in the patients who experienced an ADE.

Kishk et al[14] conducted a retrospective matched cohort study comparing children who had delirium (n = 15) as assessed by the CAPD scores of 9 or higher to those without delirium (n = 15). In this study, antipsychotic treatment included haloperidol (n = 6), risperidone (n = 6), quetiapine (n = 1), or combination therapy (quetiapine/risperidone, n = 1; risperidone/haloperidol, n = 1). The median age of those receiving haloperidol was 0.66 years. In their delirium protocol, IV haloperidol was initiated for hyperactive delirium or those who received nothing by mouth (NPO). Although a dosing protocol was used, the specific doses were not reported (Table 1). They performed an ECG to assess for QTc prolongation at baseline and then daily until patients achieved stable antipsychotic therapy and if other medications associated with QTc prolongation were added. The length of delirium for those receiving haloperidol was a median (interquartile range [IQR]) of 6 days (5.5–10 days); however, the specific duration of haloperidol and the use of a tapered prior to discontinuation were not reported. All patients had a reduction in their CAPD scores within 24 hours following initiation, with a median (IQR) decrease of 6 points (5–10 points) in patients receiving haloperidol. No patients experienced an ADE. The study design made it difficult to understand the outcomes for patients receiving haloperidol and risperidone or quetiapine as these are reported. In addition, the small sample sizes within each treatment group make it impossible to compare outcomes between agents.

Haloperidol Summary. The available literature describes 131 pediatric patients with delirium who received haloperidol. Most reports described the use of IV haloperidol in doses ranging from 0.003 to 0.278 mg/kg per dose for a duration of 3 to 22 days. One can conclude that haloperidol is effective for delirium, but the risk versus benefit must be weighed because it is

associated with unacceptable ADEs. A total of 19 of the 131 patients receiving haloperidol (14.5%) experienced an ADE, with dystonia being the most common.

Quetiapine. Quetiapine results are shown in Table 2. Turkel et al[15] performed a retrospective study of 110 children (mean age of 10.8 years) who were receiving antipsychotics for a diagnosis of delirium. A total of 19 patients (17.3%) received quetiapine; other patients received olanzapine (n = 78; 70.9%) and risperidone (n = 13; 11.8%). Delirium was assessed using the Delirium Rating Scale-Revised-98 (DRS-R-98), which includes 16 items with a maximum score of 46 points. This tool is not validated to assess delirium in critically ill children. The DRS-R-98 was retrospectively calculated for each patient based on documented psychiatric evaluations by the inpatient child psychiatry team. The authors provided limited information on the weight-based dosing these patients received or how the daily dose was divided. They did note that the mean (range) initial daily dose of quetiapine was 30 mg/day (12.5–100 mg/day) and was titrated to a mean (range) maximum daily dose of 75 mg/day (12.5–300 mg/day). Patients received quetiapine for a mean of 35.1 days (range, 1–108 days). There was no mention of whether the quetiapine was tapered prior to discontinuation. The mean change in DRS-R-98 after quetiapine administration was 12.4 ± 5.2. No ADEs were noted.

Traube et al[16] reported a case series in 4 critically ill, mechanically ventilated children, ranging in age from 0.67 to 14 years, who received quetiapine for delirium. Delirium was noted within 2 to 5 days of PICU admission according to the CAPD screening tool. The CAPD scores were not provided, but based on the description of symptoms all patients appeared to be exhibiting hyperactive delirium. Two patients received dexmedetomidine in place of a benzodiazepine, but had no resolution of delirium symptoms; hence, quetiapine was begun. In addition, non-pharmacologic measures (e.g., bringing in items from home and sleep hygiene) and music therapy were initiated in 2 of the patients without success. QTc was assessed each day in all patients. Because of unresolved delirium, all children were initiated on enteral quetiapine 0.43 to 0.7 mg/kg per dose every 8 hours. An as-needed 0.5 mg/kg per dose of quetiapine was available for administration every 6 hours for breakthrough symptoms of delirium. An improvement in delirium symptoms within 24 hours was reported in all cases, as well as a decrease in requirement of narcotics and sedatives. Doses were increased during the course of 2 to 3 days, and the maximum daily dose ranged from 0.73 to 2.8 mg/kg per dose every 8 hours or a maximum of 100 mg/day. All patients responded to quetiapine within 24 hours, but it appeared that most required a higher dose to achieve symptom resolution. Patients were continued on quetiapine for 9 to 20 days, and 2 patients were discharged on a quetiapine taper. No ADEs, including QTc prolongation, were reported.

Traube et al[17] described a case series involving 4 children, ranging in age from 0.58 to 3 years, who were admitted to the PICU, status postsurgical resection of a neuroblastoma. All patients had a diagnosis of delirium using the CAPD screening tool between postoperative days 2 and 6. The CAPD scores were not provided, but based on patient symptoms 3 exhibited hyperactive delirium and 1 child exhibited mixed delirium. Non-pharmacologic measures were initiated in any children, but all 4 were begun on quetiapine for refractory delirium. Although no dosing information was provided, the authors noted that symptoms improved in 2 patients within 24 hours after initiation of quetiapine. The other 2 patients had improvement, but a time frame was not provided. In addition, the total duration was not included for all patients, although 1 patient was continued on quetiapine for 10 days and tapered off the medication prior to discharge. No ADEs were reported.

Joyce et al[18] performed a retrospective study in 50 critically ill children with a median age of 4.5 years who were receiving quetiapine for delirium. The primary objective was to assess the safety of quetiapine. All patients were screened for delirium using the CAPD tool. The QTc interval was assessed, but the authors failed to note how often an ECG was measured. The authors also did not report the PICU day on which quetiapine was initiated and initial dose. Approximately 2428 doses of quetiapine were administered, with 39.2% of them administered in children younger than 2 years. The median dose (IQR) administered was 0.43 mg/kg per dose (0.13–0.77 mg/kg per dose) every 8 hours. The median (IQR) duration of therapy was 12 days (4.5–22 days), and there was no mention of whether the quetiapine was tapered prior to discontinuation. Three patients (6.0%) experienced an ADE of QTc prolongation; these patients were receiving 3.3 to 6.3 mg/kg/day, a higher dose of quetiapine compared with 0.5 mg/kg per dose every 8 hours. The QT prolongation improved on repeat assessment in 1 patient who had a dose reduction and 2 patients who remained on the same dose. The third patient also had improvement of the QTc on repeat assessment despite no change in their dose, but this patient died because of a withdrawal of life support. No instances of clinically significant dysrhythmias (e.g., torsade de pointes), NMS, or EPS were reported. The authors concluded that quetiapine was safe for short-term use. A limitation to this retrospective review is that the authors only assessed safety; therefore, there was no mention on the effect of quetiapine on the resolution of delirium symptoms as evidenced by reduction in CAPD scores.

Groves et al[19] reported a case series in 3 critically ill premature infants in the NICU who were receiving enteral quetiapine for delirium. Two patients were assessed for delirium using the CAPD tool, and the exact time frame for development of delirium was

not described. An ECG was performed in all patients at baseline and then every 48 hours. More frequent monitoring was conducted in patients with a prolonged QTc interval. All patients were initiated on quetiapine 0.5 mg/kg per dose every 8 hours. One patient required a dose increase to 0.5 mg/kg per dose every 6 hours because of breakthrough episodes of delirium. Of the 2 patients who had CAPD scores assessed, their symptoms improved within 72 hours, and their respective CAPD scores decreased from a 15 to 18 range to a 7 to 9 range, and from a 12 to 14 range to a 3 to 7 range, within 3 to 5 days after quetiapine initiation. In the third patient, clinical improvement was noted within 48 hours. The total duration of quetiapine was not provided, but it appears that these patients received quetiapine for at least 2 weeks to 2 months. One patient had their quetiapine tapered prior to discontinuation, but the other 2 patients were transferred to an outside facility before their quetiapine was discontinued. No ADEs were reported. This report highlights some preliminary efficacy and safety data for infants. All 3 had symptom improvement within 2 to 3 days after quetiapine initiation. In addition, it appears that these patients tolerated a prolonged course of quetiapine, ranging from 2 weeks to 2 months.

As noted above, Kishk et al[11] retrospectively evaluated children who received haloperidol, risperidone, or quetiapine for delirium as assessed by the CAPD tool. Only 2 patients received quetiapine, one as monotherapy and one combined with risperidone; both of these patients were age 14 years. For the child receiving combination therapy, it was not clear if the child was initiated on both agents at the same time or if one was added because of a lack of response. In the delirium protocol, quetiapine was initiated in patients 10 to 17 years of age with hypoactive or mixed delirium (Table 2); however, the specific doses were not reported. The authors noted the length of delirium for those receiving quetiapine was 3 days for the child receiving monotherapy and 12 days for the child requiring combination therapy. There was no mention of whether the quetiapine was tapered prior to discontinuation. Patients receiving monotherapy and combination therapy had a reduction of CAPD scores within 24 hours following initiation, by 13 and 7 points, respectively. No patients were noted to have an ADE. Because of the small number of children receiving quetiapine, it is difficult to compare the efficacy of quetiapine monotherapy or in combination on delirium symptoms.

Quetiapine Summary. The use of quetiapine to treat delirium has been reported in a total of 82 infants and older children. These studies suggest that quetiapine has a good safety profile with only three (3.7%) patients experiencing QTc prolongation, but none developed torsade de pointes. For those reports including the dose and duration, the weight-based dose ranged from 0.43 to 2.8 mg/kg per dose every 8 hours; however, 1 patient was increased to every 6 hours based on persistent symptoms. The duration was 9 days to approximately 2 months. Most of the reports described the use of a validated tool like the CAPD to assess delirium and reported improvement in scores with quetiapine. The reports describing the timeframe of symptom improvement, commonly noted improvement within 24–72 hours after initiation.[14,16,17,19]

Olanzapine. Olanzapine results are shown in Table 3. As noted above, Turkel et al[15] retrospectively evaluated the use of olanzapine in 78 children with a mean age of 10.8 years. All had delirium as assessed using the DRS-R-98. The mean initial daily dose of olanzapine was 4 mg/day (range, 0.625–30 mg/day) and was titrated to a mean maximum daily dose of 10 mg/day (range, 1.25–60 mg/day). Patients received olanzapine for a mean of 26.5 days (range, 1–132 days). There was no mention of whether the olanzapine was tapered prior to discontinuation. The mean change in DRS-R-98 after olanzapine administration was 15.7 ± 5.6. One patient experienced an ADE (1.3%) involving mild dystonia, which resolved when the dose was decreased. No other ADEs, including metabolic derangements, were noted, despite the prolonged use in some patients. The authors provided little information on the weight-based dosing used in these patients. Another limitation is that there are insufficient data supporting the use of the DRS-R-98, specifically in the PICU population.

Sassano-Higgins et al[20] conducted a retrospective study of 59 children (mean age, 9.2 years) admitted to the PICU who developed delirium during a 4-year time frame. The DRS-R-98 scale was applied retrospectively to assess delirium severity. The control group (n = 28) was composed of children with a diagnosis of delirium who did not receive any antipsychotic medication. Thirty-one children received oral or sublingual dosage formulations of olanzapine. The initial dose of olanzapine was 0.625 mg once to twice daily for infants, 1.25 mg once to twice daily for toddlers, and 2.5 to 5 mg once to twice daily for older, larger, or extremely agitated children. When needed, patients were also administered a dose of olanzapine that ranged between 50% and 100% of their starting dose each hour. A daily dose was then determined based on the amount of olanzapine required for symptom control from the previous 24 hours. After controlling for initial delirium severity, there was significant improvement in significant delirium symptoms in the olanzapine versus control group ($F_{1,20}$ = 28.62, r = 0.77, 95% confidence interval, 0.50–0.90). No significant ADEs were noted. The authors did not comment on either the duration of olanzapine therapy or the use of tapering prior to its discontinuation. Limitations of this study include the lack of randomization and patient-specific olanzapine dose information. In addition, there are limited data on the applicability of the DRS-R-98 in the PICU setting, and retrospective application of this tool could overes-

timate or underestimate delirium severity.

Turkel et al[21] conducted a retrospective study of 19 children younger than 3 years with pediatric delirium. Delirium was assessed retrospectively using the DRS-R-98, assessed before and after antipsychotic treatment. The median age of those receiving olanzapine was 1.6 years. A total of 16 children received olanzapine, whereas the remaining 3 received risperidone. The initial median daily dose of olanzapine was 1.25 mg/day (range, 0.5–20 mg/day), which was titrated to a maximum daily dose of 3.75 mg/day (1.25–35 mg/day). This daily dose was administered every 12 to 24 hours. The median duration of olanzapine was 23 days (range, 1–151 days), and there was no discussion on whether olanzapine was tapered. All children had improvement in symptoms as noted by the significant decrease in the mean DRS-R-98 between before versus after antipsychotics, 10.6 ± 2.4 ($p < 0.001$). The authors collected ADEs, including abnormal muscle tone, movement abnormalities, and arrhythmias; no ADEs were noted. This report provides some data pertaining to olanzapine efficacy and safety in younger children younger than 3 years, but it is difficult to determine the effect of olanzapine versus risperidone because the data pertaining to the DRS-R-98 for before versus after antipsychotics was combined. Limitations would include the lack of weight-based dosing and retrospective application of the DRS-R-98.

Olanzapine Summary. These reports provide some efficacy and safety data for olanzapine for use in pediatric patients with delirium. Only 1 of 125 children (0.8%) experienced an ADE (i.e., dystonia). None of these reports provided a weight-based dose or clearly specified the dosing frequency that was used. The daily dose ranged from 0.625 to 60 mg/day. The duration ranged from 1 to 151 days. All 3 reports used the DRS-R-98 to assess delirium, but there was no documentation of time to symptom improvement.

Risperidone. Risperidone results are given in Table 4. Schieveld et al[11] conducted a retrospective study on children with delirium who received risperidone as discussed previously in the haloperidol section. A total of 10 patients (median age, 7 years) were initiated on risperidone, which was given enterally. The authors noted the planned initial (0.1–0.2 mg) and maintenance (0.2–2 mg/day) doses, but they failed to provide the actual dose given. They also failed to report the duration of therapy and use of a taper prior to discontinuation. Although delirium was determined by a child neuropsychiatrist, a validated delirium assessment tool was not employed. A total of 4 of the risperidone patients (40%) were noted to have hyperactive delirium, whereas 2 (20%) developed hypoactive delirium and 4 (40%) mixed delirium. No patients experienced an ADE. These data provide limited support for dosing and efficacy of risperidone in the treatment of delirium.

As discussed in the olanzapine and quetiapine sections, Turkel et al[15] retrospectively evaluated the use of risperidone for delirium in 13 children with a mean age of 8.6 years. Delirium was assessed using the DRS-R-98. The mean initial daily dose was 0.6 mg/day (range, 0.25–1 mg/day). Dosage was titrated to a mean maximum daily dose of 1 mg/day (range, 0.25–2 mg/day). Patients received risperidone for a mean of 17.5 days (range, 2–54 days), but there was no mention of whether the risperidone was tapered prior to discontinuation. The mean change in DRS-R-98 after risperidone administration was 15.3 ± 6.0. No patients developed an ADE. As noted previously, these authors did not provide data on weight-based dosing but did provide some data pertaining to the efficacy of risperidone.

Turkel et al[21] conducted a retrospective study of 3 children with a median age of 1.6 years who were receiving risperidone for delirium as assessed retrospectively using the DRS-R-98. The median initial daily dose was 0.25 mg/kg (range, 0.1–0.25 mg/kg), which was titrated to a maximum dose of 0.25 mg/day (range, 0.1–0.5 mg/day). This daily dose was administered every 12 or 24 hours. The median duration of risperidone was 25 days, with a range of 2 to 151 days. There was no discussion on whether risperidone was tapered prior to discontinuation. All children had improvement in symptoms; as noted, there was a significant decrease in the DRS-R-98 between before versus after antipsychotics, 10.6 ± 2.4. No ADEs were reported. This report provides some data regarding the efficacy and safety of olanzapine in children younger than 3 years; however, it is difficult to determine the difference between risperidone versus olanzapine therapies. Additional limitations include the lack of weight-based dosing and retrospective application of the DRS-R-98.

As noted in the haloperidol and quetiapine sections, Kishk et al[14] conducted a retrospective study that included 6 children (mean age, 1.6 years) receiving risperidone monotherapy and 2 children (mean age, 7 years) receiving a combination therapy of risperidone plus either quetiapine or haloperidol. Per their dosing protocol, risperidone was initiated for hypoactive or mixed delirium in children of all ages, but the patient-specific dosing was not provided. As noted, they had a baseline QTc followed by a daily QTc interval assessment until patients achieved stable antipsychotic therapy and if additional QTc-prolonging medications were added. All patients had symptom improvement within 24 hours of risperidone initiation. The length of delirium for those receiving risperidone monotherapy was a median of 3.5 days (range, 2–6 days), compared with 5 to 12 days for the 2 children receiving combination therapy. There was no mention of whether the risperidone was tapered prior to discontinuation. Both the monotherapy and combination therapy patients had a reduction of CAPD scores within 24 hours following initiation, by a median of 9 points (range, 4–14 points) and 9 points (range, 7–14 points), respectively.

No patients were noted to have an ADE. These data provide some information regarding the efficacy and safety for risperidone, but it is difficult to compare the efficacy of monotherapy versus combination therapy on delirium symptoms.

Risperidone Summary. A total of 34 patients received risperidone from the included reports. No patients experienced an ADE. None of these reports provided a weight-based dose or clearly stated the dosing frequency that was used. The daily dose ranged from 0.1 to 2 mg/day. The duration ranged from 2 to 151 days. Three of the reports used the DRS-R-98 or CAPD to assess delirium. For the 1 report that documented time to symptom improvement, all achieved improvement within 24 hours, and delirium resolved within 3.5 to 12 days.[14]

Discussion

Delirium in the PICU and NICU settings has garnered more attention in recent years. This is evidenced by the fact that pediatric-specific delirium tools like the CAPD, psCAM-ICU, and pCAM-ICU have been developed within the last 6 years.[4–6] As a result of increased awareness, the prevalence of delirium in critically ill pediatric patients is on the rise. Despite this, there are limited studies evaluating the prevention and treatment of delirium in these patients. As noted in our systematic review, most reports included haloperidol and olanzapine.[9–15,20,21] Importantly, all reports included antipsychotic initiation for treatment of delirium, so the role of antipsychotics in prevention of delirium in the pediatric population has not been elucidated. It is equally important to note that although some investigators included multiple antipsychotics in their reports, no prospective studies directly compared the safety and efficacy of these antipsychotics. Only 2 studies included an evaluation of the different delirium categories (e.g., mixed or hypoactive), so it is difficult to determine which antipsychotic would be the best choice based on delirium subtype.[8,11] Many of the studies were limited by small sample size and lack of information about weight-based dose and/or dosing frequency.

Assessment Tools. Nine of the studies included a tool to assess the efficacy of agents in treating delirium.[13–21] As noted, the only 3 validated tools to assess delirium in critically ill children are CAPD, psCAM-ICU, and pCAM-ICU.[4–6] Five reports used the CAPD tool in assessment, but no reports described the use of the psCAM-ICU or pCAM-ICU.[14,16–19] The remaining 4 reports used the DRS-R-98[15,20,21] or the SOS-PD[13]; neither of these tools has been validated in the pediatric ICU settings. Although these reports did use an objective tool to assess delirium, it is difficult to determine the true efficacy of the antipsychotics in this setting because these tools have not been validated. Many of the reports were not specific on the frequency with which these assessment tools were used. In 2016, the European Society for Pediatric and Neonatal Intensive Care released guidelines on pain, sedation, withdrawal, and delirium in children that recommended clinicians use a validated assessment tool every 12 hours in critically ill children.[7] It should be noted that none of these screening tools were developed to, and hence do not, assess the severity of delirium. That being said, clinicians could use these tools to supplement their clinical examination to assess the effect of antipsychotic initiation.

Adverse Effects. A total of 23 of the 370 patients (6.2%) experienced an ADE from haloperidol (14.5%), quetiapine (3.7%), or olanzapine (0.8%). No patients with risperidone had an ADE, including the 2 patients who received combination therapy with quetiapine or haloperidol.[14] A total of 13 patients (56.5%) had dystonia that resolved with either an antipsychotic dose reduction, antipsychotic discontinuation, and/or anticholinergic administration.[9–12,15] A total of 4 patients (17.4%) receiving haloperidol developed EPS, and another 2 (8.7%) developed oversedation; these patients were also managed with haloperidol discontinuation, haloperidol dose reduction, and/or anticholinergic administration.[13] A total of 3 patients (13.0%) receiving haloperidol developed either hyperpyrexia and/or NMS; these symptoms resolved in 2 patients with haloperidol discontinuation or administration of dantrolene.[10,12] The other patient with NMS died despite administration of diphenhydramine and benztropine. Only 3 patients (13.0%) with ADEs developed QTc prolongation.[18] All 3 had improvement in QTc prolongation, but 1 did require reduction of the quetiapine dose. Importantly, no patients developed torsade de pointes.

Antipsychotics have been associated with other significant ADEs that were not assessed in studies included in this review. Common ADEs include oversedation, agitation, and orthostatic hypotension. As noted earlier, a few patients had oversedation, but no reports of orthostatic hypotension were mentioned. It is difficult to evaluate the effect of the antipsychotics on increased agitation in our review because all of the patients were noted to have a diagnosis of delirium that may have included agitation at baseline. The second-generation antipsychotic agents have been associated with a number of cardiometabolic ADEs, including dystonia, dyslipidemia, and hyperglycemia.[22,23] Correll et al[23] conducted a prospective cohort study in 257 children aged 4 to 19 years receiving chronic administration of risperidone, olanzapine, quetiapine, or aripiprazole for a median of 10.8 weeks for non-delirium indications. All agents were associated with significant weight gain (4.4–8.5 kg vs 0.2 kg in controls). Olanzapine and quetiapine were associated with significantly higher total cholesterol, triglycerides, and non–high-density lipoprotein cholesterol values than controls, whereas risperidone was only associated with significantly higher triglycerides concentrations. None of the studies in our systematic review evaluated these effects; how-

Table 5. Summary of Dosing Regimens Described in Reported Studies[9–21,27] and Commercially Available Dosage Formulations

Agent	Dosing Range	Dosage Formulations
Haloperidol	0.003–0.278 mg/kg/dose*	IM haloperidol decanoate solution (50, 100 mg/mL) IV haloperidol lactate solution (5 mg/mL) Oral haloperidol liquid concentrate (2 mg/mL) Oral tablets (0.5, 1, 2, 5, 10, 20 mg)
Quetiapine	0.432.8 mg/kg/dose every 8 hr† enterally	Immediate-release tablets (25, 50, 100, 200, 300, 400 mg) Extended-release tablets (50, 150, 200, 300, 400 mg)
Olanzapine	0.625–60 mg/day enterally	IM reconstituted solution (10 mg) IM reconstituted suspension (210, 300, 405 mg) Oral tablets (2.5, 5, 7.5, 10, 15, 20 mg) Oral disintegrating tablets (5, 10, 15, 20 mg)
Risperidone	0.1–2 mg/day enterally	IM reconstituted suspension (12.5, 25, 37.5, 50 mg) Oral solution (1 mg/mL) Oral tablets (0.25, 0.5, 1, 2, 3, 4 mg) Prefilled subcutaneous syringe (90, 120 mg)

* Most reports used IV administration.
† One patient's dose changed to every 6 hr based worsening delirium.

ever, some patients received quetiapine, risperidone, and olanzapine for up to 151 days, so it is plausible that these metabolic effects could have occurred in some patients had these laboratory studies been assessed.

Many clinicians are aware that neurologic ADEs, like dystonia, EPS, agitation, and NMS, can occur with antipsychotics. However, we would advocate for additional routine monitoring for some of the lesser-known ADEs when administering these agents. No reports documented orthostatic hypotension in any patient, although it was not clear if this was evaluated in all the reports. As more and more PICUs consider the use of early mobility strategies in children, we would advocate for increased awareness and recommend slow transitions from sitting to standing to prevent symptoms of light-headedness and to prevent falls when ambulating. Second, in patients who receive second-generation antipsychotics for longer than 8 weeks, we would recommend routine screening for cardiometabolic ADEs (ie, total cholesterol, triglycerides, and non–high-density lipoprotein cholesterol). The American Diabetes Association and American Psychiatric Association recommend obtaining weight at baseline and again at 4, 8, and 12 weeks after initiation of antipsychotics in order to assess for weigh gain.[24,25] In addition, they recommend an a fasting plasma glucose, blood pressure, and a fasting lipid panel 3 months after initiation; if these parameters are abnormal they recommend periodic assessments as clinically indicated. These recommendations were intended for patients receiving second-generation antipsychotics for other psychiatric diagnoses requiring prolonged therapy and not for acute delirium in the PICU/NICU setting. However, as noted in our review, some patients received antipsychotics for up to 5 months, so clinicians should consider implementing this cardiometabolic screening for children with prolonged PICU/NICU stays who require extended treatment of delirium.

Third, because of the risk of QTc prolongation for antipsychotics, clinicians should consider routine monitoring with ECGs to prevent the development of torsade de pointes. Some sources have evaluated the potential of QTc prolongation with antipsychotics and designated them as known risk, possible risk, and conditional risk; of those we have evaluated in this review, they classified haloperidol with known risk, risperidone with possible risk, and quetiapine/olanzapine with conditional risk.[26] Only 6 reports used an ECG to assess for a prolonged QTc interval,[12–14,16,18,19] and there was variability in the frequency of QTc monitoring among these reports. Most of these reports assessed an ECG at baseline and then again every 24 to 48 hours. Because the remainder of the reports did not mention if an ECG was obtained, it is difficult to determine the true incidence of QTc prolongation. Although quetiapine has a lower risk of QTc prolongation than haloperidol, it was the only agent associated with QTc prolongation in these reports. Until further recommendations are developed, a reasonable approach would be to assess baseline ECGs and then every 48 to 72 hours or more frequently depending on the patient's risk factors and concomitant use of other medications known to cause QTc prolongation. Any patient with a prolonged QTc interval (i.e., QTc >450 ms or a 25% increase from baseline) should have more frequent ECG monitoring as well as consideration for a reduction in dose or discontinuation of antipsychotics.[25]

Table 5 provides a summary of the dosing ranges reported in our systematic review and the commercially available dosage formulations.[9–21,27] As noted, there was variability in the dosing among all of the reports. It is difficult to use these data to make spe-

cific recommendations for patients with PICU/NICU delirium considering the weight-based dosing and specific dosage formulation were not articulated in all reports. Haloperidol, olanzapine, and risperidone are all available as an injectable formulation; however, the IM formulation should be avoided if possible in children with PICU/NICU delirium because administration of IM medications may induce pain and increased agitation in children with delirium.[27] For patients who are NPO, clinicians could consider IV haloperidol lactate or olanzapine or risperidone oral disintegrating tablets. However, IV haloperidol is associated with a higher risk of QTc prolongation compared with other antipsychotics, and oral disintegrating tablet use would be limited for younger children and infants because of the fixed dosage formulations (Table 5).[26,27] All agents are available as oral immediate release tablets, and haloperidol and risperidone are available as an oral liquid solution.[27] Quetiapine is only available as an oral tablet. Some extemporaneous formulation recipes have been published, but to date no studies have evaluated stability.[27,28] The flexibility in these formulations is helpful because it is necessary to taper patients on prolonged courses (e.g., >10 days) of these antipsychotics to prevent akathisia and dyskinesias that have been reported with abrupt antipsychotic discontinuation.[29] It is difficult to comment on whether any patient experienced drug withdrawal because only 3 reports mentioned tapering, and all patients were receiving quetiapine.[16,17,19] Few reports described tapering, and for these reports that indicated the dose was tapered, there was no mention of the tapering process and what dosage formulations were used to accommodate the changing dose.

Conclusions

Based on our review, haloperidol, quetiapine, olanzapine, and risperidone have a potential role for treatment of delirium in critically ill children. This review has several limitations: (1) most available literature included comprised case reports or retrospective studies with a small sample size; (2) weight-based dosing information was not consistently provided; (3) some reports failed to note the product formulation used; (4) the use of antipsychotics tapering and tapering process was not described; (5) frequently the use of a validated delirium scoring was lacking; and (6) there was great variability in the assessment and reporting of adverse drug events.

Our systematic review includes some limited evidence for the treatment of delirium in critically ill children with haloperidol, quetiapine, olanzapine, and/or risperidone. A previous study found some preliminary evidence to support the use of quetiapine to prevent delirium in adults, but currently no such studies have supported this finding in children.[30] It seems reasonable that these agents may be administered for children with delirium who have failed non-pharmacologic measures. Because there are no randomized studies comparing one antipsychotic versus another in our review, it is difficult to recommend one of these agents over another. The selection of an antipsychotic should be based on patient-specific factors (e.g., risk of QTc prolongation, NPO status, weight, and age). For children weighing less than 10 kg, it may be difficult to select the proper dose and dosage based on commercially available products. In this case, clinicians could consider the use of haloperidol or risperidone because they are available as an oral liquid formulation. Alternatively, clinicians could consider splitting the immediate-release tablets of quetiapine or olanzapine into one-quarter or one-half tablets. Monitoring should include the use of a delirium assessment tool that has been validated for the PICU/NICU population (i.e., CAPD, psCAM-ICU, and pCAM-ICU), and assessment should occur a minimum of every 12 hours.[1] Short-term ADEs include orthostatic hypotension, oversedation, NMS, EPS, or QTc prolongation. Monitoring for cardiometabolic ADEs should be considered for patients receiving more than 8 weeks of antipsychotics. Finally, withdrawal symptoms, such as akathisia and dyskinesias, have been reported, so clinicians should consider tapering in children receiving more than 10 days of therapy. Anecdotally, the authors of this systematic review taper the antipsychotic every 72 hours by either decreasing the dose or changing the dosing interval for children receiving an oral liquid formulation. For children receiving tablets, we adjust the dosing interval every 72 hours. Future studies should elucidate the role of antipsychotics for prevention and treatment of delirium to determine the true effect of these agents on decreasing the burden of delirium in children.

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