Antipsychotic Treatment of Delirium in Critically Ill Children: A Retrospective Matched Cohort Study

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OBJECTIVE To describe the use of pharmacologic treatment in critically ill children treated according to a delirium protocol and compare those treated with antipsychotics to those treated non-pharmacologically.

METHODS The study included a retrospective matched cohort describing patients who were pharmacologically treated for delirium compared to those with delirium but not treated in a PICU from December 2013 to September 2015, using a delirium management protocol. Patients were matched by age, sex, diagnosis, mechanical ventilation (MV), and presence of delirium.

RESULTS Of 1875 patients screened, 188 (10.03%) were positive for delirium. Of those, 15 patients (8%) were treated with an antipsychotic for delirium. Patients with delirium treated with antipsychotics were younger, had more delirium days (6 vs. 3, $p=0.022$), longer MV days (14 vs. 7, $p=0.017$), and longer PICU length of stay (34 vs. 16 days, $p=0.029$) than in the untreated group. Haloperidol, risperidone, and quetiapine were used in 9, 6, and 2 patients, respectively. Two patients were treated with multiple antipsychotics. Antipsychotic treatment was initiated on day 2 of delirium for 8 of 15 patients (53.3%). Ten patients in the treatment group had improved delirium scores by day 2 of treatment. No significant differences in sedation exposure between groups. No significant adverse effects were reported.

CONCLUSIONS No significant adverse events seen in this small cohort of critically ill pediatric patients with delirium treated with antipsychotic therapy. Patients with early-onset delirium refractory to non-pharmacologic treatment may have a more effective response to antipsychotic therapy than patients with late-onset refractory delirium.

ABBREVIATIONS CAPD, Cornell Assessment of Pediatric Delirium; EKG, electrocardiogram; EPS, extrapyramidal symptoms; ICU, intensive care unit; MV, mechanical ventilation; PCPC, pediatric Cerebral Performance Category; PIM, Pediatric Index of Mortality, PICU, pediatric intensive care unit; RCT, randomized control trial

KEYWORDS antipsychotics; critical illness; delirium; haloperidol; pediatric; quetiapine; risperidone

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Introduction

Delirium is an acute, fluctuating disturbance of cognition and consciousness that is triggered by a serious medical illness and not explained by a preexisting, established, or evolving neurologic disorder.¹ In critically ill adults, delirium is well studied and widely accepted as a major public health problem; however, delirium has not been considered a pediatric illness until recently.² Over the last decade, delirium has been increasingly identified in critically ill pediatric patients, largely due to the development of pediatric screening tools such as the Cornell Assessment of Pediatric Delirium (CAPD), which is validated in critically ill children aged 0 to 18 years.^{3–10}

Although the primary treatment for delirium includes management of the underlying cause (e.g., acute critical illness) and prevention of iatrogenic factors (e.g., polypharmacy, pain, sleep deprivation, immobility),

some children require antipsychotic therapy to manage symptoms of delirium. Antipsychotic therapy may be helpful in reducing agitation, confusion, sleep-wake disturbance, and the duration of delirium symptoms.⁶ Little information exists about the most effective pharmacologic treatment for delirium in children. Antipsychotics are frequently used for the treatment of adult delirium,¹¹ but evidence describing their use in children is limited and includes small retrospective reviews and case reports.^{3,12–17} Common agents used include haloperidol, risperidone, and quetiapine, although currently there are no Food and Drug Administration–approved antipsychotic medications to treat delirium in adults or children.¹⁸ Common adverse effects of antipsychotic therapy include sedation, agitation, orthostatic hypotension, and anticholinergic effects (e.g., dry mouth and constipation). Less common but more serious adverse effects include electrocardiographic abnormalities like

QT segment prolongation and ventricular arrhythmias (torsades de pointes), extrapyramidal symptoms (EPS), seizures, and neuroleptic malignant syndrome.⁶ Therefore, to promote optimal and safe treatment of delirium, close monitoring for potential adverse effects (e.g., vital statistics, neurologic assessment, electrocardiogram [EKG] and laboratory analysis) and collaborative management with pediatric subspecialists including psychiatry and pharmacy is warranted.¹⁹

At the University of Maryland Children's Hospital, an interprofessional team of critical care intensivists, nurse practitioners, nurses, psychiatrists, and pharmacists developed a comprehensive protocol to prevent, identify, and treat delirium in the pediatric intensive care unit (PICU). The protocol consists of a validated delirium assessment tool, non-pharmacologic prevention strategies, identification of potential etiologies, pharmacologic treatment, and monitoring for adverse events.²⁰ The purpose of this study is to describe the use of antipsychotic treatment in critically ill children treated according to our delirium protocol and to compare those treated pharmacologically with those treated non-pharmacologically.

Materials and Methods

Setting and Population. This study was a retrospective matched cohort study describing all patients who were treated with antipsychotic pharmacologic treatment for delirium in comparison with those scoring positive for delirium but not treated pharmacologically. The patients were matched by age, sex, diagnosis, mechanical ventilation (MV), and presence of delirium. The study collected data from a single PICU in an academic tertiary hospital from December 1, 2013, through September 30, 2015, during the implementation of an intensive care unit (ICU) bundle that included a delirium protocol, sedation protocol, and early mobilization protocol.²⁰ This study was a planned secondary analysis of the ICU bundle patient cohort. Data presented in this study have not been previously published. The study was approved by the institutional review board at the University of Maryland Medical Center, and informed consent was waived.

Endpoints. The primary endpoints of this study were the utilization of sedation medications before and after a delirium-positive screen. The utilization of sedation medications was compared between the antipsychotic-treated group versus the non-treated group (no exposure to antipsychotics). Secondary endpoints included presence of adverse effects in the antipsychotic treated patients: prolongation in QT segment, arrhythmias, seizures, EPS, or neuroleptic malignant syndrome.

Delirium Protocol Description. The delirium protocol was implemented in December 2013 and consisted of pediatric validated pain, sedation, and delirium assessment instruments; non-pharmacologic prevention strategies; identification of potential delirium etiologies;

pharmacologic treatment; and monitoring for adverse events when antipsychotic therapy was initiated.²⁰ Based on our experience in managing critically ill children with delirium in our PICU and available literature, any medication changes were discussed and approved within a multidisciplinary team that included a pediatric psychiatrist, pediatric ICU attending, ICU nurse practitioner, and pediatric clinical pharmacist specialist. Individual considerations such as liver function, drug-drug interactions, ability to tolerate enteral medications, and previous response to medications factored into antipsychotic choice; however, the algorithm provided our main framework. The pharmacologic agents we used in our delirium algorithm were haloperidol, risperidone, and quetiapine. For hypoactive delirium, we used risperidone for patients <10 years old and quetiapine for patients ≥10 years old. Haloperidol was the first-line agent for hyperactive delirium and for patients unable to take enteral medications, who required intravenous use (Table 1). Antipsychotic therapy was administered as monotherapy, and medications such as diphenhydramine or benztropine were not used as prophylaxis for EPS.

Prior to initiating a patient on antipsychotic therapy, both psychiatry and pharmacy were consulted in collaboration with the PICU team to further determine if the patient had any contraindications to pharmacologic treatment of delirium (e.g., drug-drug interactions, other QTc-prolonging agents). A baseline EKG was obtained prior to initiation of antipsychotic therapy, and a daily EKG was obtained to monitor QT segment length if therapy was continued. Daily EKGs were obtained until stable antipsychotic dosing was achieved and when any medications that may prolong QTc were added. Other monitoring included baseline laboratory data such as complete blood count, electrolytes, and metabolic panel. In addition to monitoring for changes in vital signs, pain and sedation scores, and neurologic assessment, nurses were educated to assess for signs and symptoms suggestive of neuroleptic malignant syndrome, including hyperthermia, acute mental status change, autonomic instability, and muscle rigidity. Such symptoms necessitated immediate notification of the interdisciplinary team (PICU medical provider, psychiatrist, and clinical pharmacist), discontinuation of antipsychotic therapy, and treatment of adverse effects.

Delirium Phenotype. Delirium was assessed using the validated CAPD screening tool, which consists of 8 items scored on a scale of 0 to 4 (0 = "always," 4 = "never").^{4,5} A CAPD score of 9 or greater represents a positive delirium screen; diagnosis of delirium was then confirmed by a PICU physician or psychiatrist. The type of delirium was determined by assessing the patient's psychomotor activity and level of alertness using our PICU standard of care sedation assessment tools in combination with the CAPD scored items. If the patient's sedation score was consistent with deep

Table 1. Pharmacologic Antipsychotic Therapy

	Receptors	Formulations	Dose	Notes
Haloperidol	Strong D ₂ agonist	IV, oral liquid, oral tablet, IM	0.05 mg/kg/day divided twice daily For urgent need: <3 years: 0.025 mg/kg; ≥3 years: 0.5–1 mg every 15–20 min until agitation controlled Maintenance dose: oral preferred: 0.05–0.15 mg/kg/day divided every 6–12 hr	Consider for hyperactive delirium or if unable to give enteral medication (IV dosing is twice as potent as enteral; use lowest dose)
Risperidone	Strong 5-HT ₂ -dopamine-D ₂ antagonist	Oral liquid, oral tablet, disintegrating tablet	<5 yr: 0.1 mg once or twice daily ≥5 yr: 0.2 mg once or twice daily	Consider for hypoactive or mixed delirium
Quetiapine	D ₂ and 5-HT ₂ antagonist and H ₂ antagonist	Oral tablet	10–17 yr: 12.5–25 mg every 12 hr	Consider for hypoactive or mixed delirium

D₂ dopamine; 5-HT₂ serotonin; H₂ histamine; IM, intramuscular

sedation or unresponsiveness, then the CAPD was not performed. For all other sedation scores, the CAPD was performed, and if the score was consistent with delirium, then the delirium type was determined by evaluating the individual item scores (ranging from “never” to “always”) and consistency with degree of alertness and psychomotor activity. Items 1 through 4 and 7 through 8 on the CAPD tool were utilized to help determine if the patient had hypoactive, hyperactive, or mixed delirium. For example, a score of 4, which corresponds with answers of “never” on items 1 through 4 and 7 and 8, was considered most consistent with hypoactive delirium. Ultimately, the identified delirium type was confirmed by a PICU physician or psychiatrist.

Sedation Protocol Description. For all mechanically ventilated patients, we used a sedation protocol to guide treatment of pain and sedation for children expected to have short-term (≤48 hours) versus prolonged (>48 hours) mechanical ventilation. The protocol outlines first-line treatment (e.g., low-dose fentanyl or dexmedetomidine infusion for short-term sedation versus fentanyl infusion and intermittent low-dose lorazepam for long-term sedation) and describes agent titration based on goal sedation and pain scores. The protocol standardizes treatment of episodic pain or agitation with appropriate bolus dosing of a narcotic or sedative agent and limits cumulative benzodiazepine exposure, if appropriate. However, deviations from the protocol are left to the discretion of the provider based on clinical assessment of the patient.

Data Collection. Delirium assessment was conducted once during a 12-hour nursing shift using the CAPD instrument⁴ and transitioned to the revised CAPD instrument in March 2014.^{5,7} Matched cases were identified by having a positive CAPD delirium score, similar age and disease process, and receiving mechanical venti-

lation, but not pharmacologic treatment, for delirium. Data collection included demographic information, admission and secondary diagnoses, Pediatric Cerebral Performance Category (PCPC), Pediatric Index of Mortality (PIM) score, days of mechanical ventilation, CAPD score, delirium days, antipsychotic treatment agent, day of delirium pharmacologic agent usage, initial dosing, and length of delirium pharmacologic treatment, along with cumulative pharmacologic doses of sedation medications such as benzodiazepines, opioids, dexmedetomidine, and clonidine, which are the drugs commonly used in our PICU in patients requiring mechanical ventilation. Benzodiazepines were converted to oral lorazepam equivalents^{21,22} and opioids were converted to oral morphine equivalents.^{23–25} Data to assess potential side effects were also collected, such as calculated QTc values to monitor for QTc prolongation, presence of seizures, EPS, and dystonic reactions.

Statistical Analysis. Data were analyzed using descriptive statistics for frequencies and ranges. To compare any differences between patients treated with and without antipsychotic therapy, Wilcoxon rank-sum test for continuous variables and chi-square test or Fisher’s exact test for categorical variables were performed. The Wilcoxon rank-sum test was used for comparison of sedation medications between those untreated and treated. For comparison in sedation medications prior to delirium, the Wilcoxon signed-rank test was performed. As a result of the small sample size, regression analysis was not appropriate for our data. Analyses were performed with SAS version 9.4 (SAS Inc, Cary, NC).

Results

Of the 1875 patients screened for delirium, 188 patients (10.03%) were positive. Of those, 15 patients (8%)

were treated with an antipsychotic for delirium. There were no differences in weight, PIM score, and PCPC between treated patients and matched controls ($p > 0.1$). Cognition at baseline was normal in 7 patients in the pharmacologically treated group versus 12 patients in the matched control group. There were 5 patients with moderate to severe developmental delay in the treated group versus 3 in the matched control group (Table 2).

Patients with delirium treated with antipsychotics (treated group) were younger, had more days of delirium (6 days versus 3 days, $p = 0.022$), longer length of mechanical ventilation (14 days versus 7 days, $p = 0.017$), and longer PICU length of stay (34 days versus 16 days, $p = 0.029$) than did those who tested positive for delirium and were not treated pharmacologically. Significantly more patients in the untreated group were discharged home ($p = 0.032$), whereas more patients in the treated group were transferred to a rehabilitation center; and 2 patients died, both receiving end-of-life care. The type of delirium was similar between pharmacologically treated and matched control groups (Table 2).

Haloperidol, risperidone, and quetiapine were used in 9, 6, and 2 patients, respectively (Figure). Two patients were treated with more than one antipsychotic; one patient received risperidone and quetiapine and the other risperidone and haloperidol. Antipsychotic treatment was initiated on day 2 of delirium for 8 of 15 patients (53.3%), but ranged from day 1 through 5 of delirium. Although both groups had positive CAPD scores, all patients in the untreated group had intermittent positive CAPD scores. Twelve of the 15 untreated patients had one positive score for 2 to 3 days beginning on day 2 of hospitalization.

The majority of the patients were treated with an antipsychotic for a short duration of time (≤ 6 days); however, 33% received an antipsychotic for > 20 days (Table 3). Ten patients in the treatment group had improved CAPD scores by day 2 of antipsychotic pharmacologic treatment. Three patients had lower CAPD scores after initiation of antipsychotic treatment but continued to have positive intermittent delirium screens (scores ranged from 9 through 12) for 11 to 26 days. Two patients received long-term antipsychotic treatment (one patient was discharged on antipsychotic therapy, one patient received end-of-life care).

Although there were no significant differences in sedation medications prior to screening positive for delirium, more patients in the treated group had received benzodiazepines, opioids, and dexmedetomidine compared with patients in the untreated group (Table 4). Table 5 shows the utilization of sedation medications in the untreated and treated groups from initial positive score for delirium until they no longer screened positive for delirium. No significant differences were seen between groups. However, treated patients received a larger median dose of benzodiazepines ($p = 0.071$) and

opioids ($p = 0.35$) than did untreated patients, whereas untreated patients received a larger median dose of dexmedetomidine than did the treated group.

No serious adverse side effects were reported in the treated patients, including prolongation in QT segment (normal defined as < 450 msec), arrhythmias, EPS, or neuroleptic malignant syndrome. One patient admitted following a near-drowning injury and with a history of Dandy-Walker malformation was noted to have seizure-like activity. The episode was described as rhythmic movement of the upper extremities occurring several hours after initiation of risperidone. A video electroencephalogram ruled out seizure activity during the episodes of rhythmic movement. A brain magnetic resonance imaging was performed and was resulted as "normal" except for presence of the Dandy-Walker malformation. The patient was continued on risperidone and treated for 5 days without further events.

Discussion

Delirium is common in the ICU, and its presence can affect both short- and long-term outcomes. Over the last decade, improvements in monitoring and assessment for pediatric delirium in the ICU have resulted in validated and reliable tools, such as arousal scales and bedside delirium-monitoring instruments.^{4,5} Once delirium has been recognized and the underlying causes and modifiable risk factors addressed, the next step in management, if delirium persists, can be the administration of antipsychotic therapy to control symptoms. Since it is hypothesized that excess dopamine and deficient acetylcholine contribute to delirium, the rationale for antipsychotics involves dopaminergic blockade.¹¹ First- and second-generation antipsychotics have a wide range of side effects and drug interactions, so to ensure that the benefits of treatment outweigh the potential harms, a multidisciplinary approach to manage patients with delirium in the ICU is paramount.

Evidence describing effective antipsychotic therapy in critically ill children with delirium remains limited. The findings of this study add further data demonstrating that with appropriate monitoring, antipsychotic therapy in critically ill children, including very young children, can be administered without serious adverse effects. This study was a subanalysis of an earlier large descriptive prospective analysis²⁰ of delirium in critically ill children, which was recently published by our group. Although our delirium prevalence was consistent with that described in earlier studies,^{4,5,10,26–28} the number of patients with delirium requiring antipsychotic pharmacologic treatment was low (8%). In general, patients were effectively managed with preventative and non-pharmacologic treatment.

Antipsychotic therapy used to treat patients with delirium that was unresponsive to non-pharmacologic

Table 2. Patient Characteristics in Matched Cohort

Characteristics	Total (n=30)	Untreated (n=15)*	Treated (n=15)†	p value
Age, mo, median (IQR)	21 (6–48)	23 (3–48)	19 (7–48)	0.88
Sex, n (%)				
Male	13 (43.3)	8 (53.3)	5 (33.3)	0.46
Female	17 (56.7)	7 (46.7)	10 (66.7)	
Weight, kg, median (IQR)	10.9 (7.823)	11.1 (5.4–24)	10.7 (8–23)	0.86
Diagnosis, n (%)				
Respiratory	17 (56.7)	9 (60)	8 (53.3)	0.71
Cardiovascular	4 (13.3)	2 (13.3)	2 (13.3)	
Oncology	2 (6.7)	0 (0)	2 (13.3)	
Neurology	4 (13.3)	3 (20)	1 (6.7)	
Infectious	2 (6.7)	1 (6.7)	1 (6.7)	
Other	1 (3.3)	0 (0)	1 (6.7)	
PIM, median (IQR)	0.4 (0.3–1.8)	0.3 (0.1–1.7)	0.4 (0.3–2.1)	0.24
PCPC, n (%)				
Normal	19 (63.3)	12 (80)	7 (46.7)	0.17
Mild	3 (10)	0 (0)	3 (20)	
Moderate	6 (20)	2 (13.3)	4 (26.7)	
Severe	2 (6.7)	1 (6.7)	1 (6.7)	
Length of mechanical ventilation, median (IQR)	8 (5–14)	7 (4–9)	14 (5–24)	0.017
Days of delirium, median (IQR)	3 (3–7)	3 (2–3)	6 (3–12)	0.022
Length of stay, median (IQR)	19.5 (11–44)	16 (10–23)	34 (17–62)	0.029
Disposition, n (%)‡				
Home	20 (69.0)	13 (92.9)	7 (46.7)	0.032
Rehab	6 (20.7)	1 (7.1)	5 (33.3)	
Hospital transfer	1 (3.5)	0 (0)	1 (6.7)	
Died	2 (6.9)	0 (0)	2 (13.3)	
Psychiatric history, n (%)				
No	26 (86.7)	13 (86.7)	13 (86.7)	1.0
Yes	4 (13.3)	2 (13.3)	2 (13.3)	
CAPD, median (IQR)	16 (14–20)	15 (14–20)	16 (14–21)	0.77
Type of delirium, n (%)				
Hyperactive	3 (10.0)	0 (0)	3 (20.0)	0.15
Hypoactive	7 (23.3)	5 (33.3)	2 (13.3)	
Mixed	20 (66.7)	10 (66.7)	10 (66.7)	

PCPC, Pediatric Cerebral Performance Category; PIM, Pediatric Index of Mortality

* Patients with delirium not treated with antipsychotics.

† Patients with delirium and treated with antipsychotic.

‡ Frequency missing = 1 in untreated.

Figure. Treated patients by age group (N = 15)*.

*Two patients received 2 agents.

■ Haloperidol; ■ Risperidone; ■ Quetiapine

strategies in our protocol included haloperidol, risperidone, or quetiapine (Table 1). Specific antipsychotic treatment was dependent on delirium subtype, patient age, and whether the patient could tolerate enteral medications. First-generation antipsychotics or “conventional” antipsychotics such as haloperidol, chlorpromazine, and thioridazine are known to have high rates of EPS side effects due to their strong dopamine D₂ antagonism, as well as extensive CYP450 metabolism, leading to the potential for multiple drug interactions.²⁹ We chose to use haloperidol because of its frequent use in the adult population, our ability to administer it intravenously, and the limited data on antipsychotic use in the PICU population at the time of the delirium protocol development.^{12,16} Second-generation antipsychotics such as risperidone, quetiapine, olanzapine, and ziprasidone have lower rates of EPS and tardive dyskinesia, but they present increased risk of weight gain, metabolic side effects, and dyslipidemia with long-term use as a result of the serotonin 5-HT₂ receptor binding exceeding affinity for D₂ receptors.^{30,31} Risperidone and quetiapine were included in our delirium treatment protocol because of their overall favorable side effect profile and increasing evidence of safe use, including small studies in critically ill children.^{6,13,14,17} Since this study period, our protocol has evolved to expand the use of quetiapine to younger children.

In our study, patients treated with antipsychotics had longer length of mechanical ventilation, longer length

of stay, and fewer were discharged home which may suggest that those needing antipsychotic treatment were more medically complex. The small n-value likely contributed to the lack of statistically significant differences between their PIM and PCPC scores. Additionally, these patients also had greater exposure to opioids and benzodiazepines than those patients with delirium who did not require antipsychotic treatment. This supports adult and pediatric evidence of benzodiazepine exposure as a risk factor for delirium and underscores an important target intervention.^{28, 31-35}

Alternatively, these outcomes can suggest that antipsychotic treatment worsened outcomes. While these results were not expected, similar outcomes are described in the adult literature with evidence questioning the efficacy of antipsychotic use. A meta-analysis of antipsychotic medication for the treatment of delirium in adults did not find evidence that antipsychotics reduced delirium duration or severity³⁶ and a randomized controlled trial (RCT) in adults receiving palliative care found that dose-titrated oral haloperidol and risperidone groups had higher delirium symptoms after 72 hours of treatment compared to placebo group.³⁷ Recently, Girard et al conducted a large, double-blind, randomized, placebo-controlled trial and found no evidence that the use of haloperidol or ziprasidone had an effect on the duration of delirium in adult patients with acute respiratory failure or shock in the ICU.³⁸ These results supported other small RCTs in adults

Table 3. Characteristics of Antipsychotic Treatment Group

Patient	Age	Primary Diagnosis	Comorbidities	Protocol Tx (Hospital Day Started)	CAPD Score		Length of		
					Before Tx	24 hr After Tx	Mechanical Ventilation (days)	Delirium (days)	Hospital Stay (days)
1	4 mo	Bronchiolitis	RPA agenesis, RLL lobectomy, CLD	Haloperidol (11)	15	10	139	Intermittent for 45 days	139
2	6 mo	Empyema, status post-VATS	None	Haloperidol (5)	14	10	14	6	36
3	8 mo	Bacterial pneumonia	Prematurity, CLD, DiGeorge Syndrome, VSD	Haloperidol (11)	16	10	27	7	51
4	19 mo	Status post-near drowning	Dandy-Walker, duodenal atresia, asthma	Haloperidol (5)	15	10	8	6	17
5	20 mo	Bronchiolitis	Reactive airway disease	Risperidone (3)	18	8	5	3	8
6	7 mo	Bacterial pneumonia, status epilepticus	Prematurity, CLD, GERD	Risperidone Haloperidol (4)	24	10	14	5	34
7	15 mo	Bacterial pneumonia	HLHS, status post-Glenn procedure, CLD	Risperidone (1)	18	9	63	5	63
8	18 mo	ALCAPA	Prematurity, CHARGE syndrome, CLD, tracheostomy	Risperidone (2)	14	8	5	2	10
9	6 mo	MSSA pericarditis	None	Risperidone (7)	15	7	10	4	33
10	4 yr	Status asthmaticus, pneumonia	Prematurity, asthma	Risperidone (3)	12	8	10	6	24
11	14 yr	MRSA septic shock	Rhabdomyolysis	Quetiapine (12)	24	11	22 (ECMO)	3	59
12	14 yr	Sepsis, ARDS	MRCP, epilepsy, nasal alveolar rhabdomyosarcoma	Risperidone Quetiapine (1)	19	12	24 (ECMO)	Intermittent for 12 days	62
13	17 yr	Methotrexate toxicity	Large B cell lymphoma	Haloperidol (2)	22	12	14	Intermittent for 13 days	74
14	3 yr	Status epilepticus	None	Risperidone (2)	21	7	2	2	6
15	3 yr	Status post-kidney transplant	Hypothyroidism, pulmonary hypoplasia, CLD	Haloperidol (6)	19	9	5	3	18

ALCAPA, anomalous origin of the left coronary artery from the pulmonary artery; ARDS, acute respiratory distress syndrome; CAPD, Cornell Assessment of Pediatric Delirium; CHARGE, coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities; CLD, chronic lung disease; ECMO, extracorporeal membrane oxygenation; GERD, gastroesophageal reflux disease; HD, hospital day; HLHS, hypoplastic left heart syndrome; LOS, length of stay; MRCP, mental retardation and cerebral palsy; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MV, mechanical ventilation; RLL, right lower lobe; RPA, right pulmonary artery; Tx, treatment; VATS, video-assisted thoracoscopic surgery; VSD, ventricular septal defect

Table 4. Distribution of Sedation Medications for Patients Prior to Delirium Positive Screen

Sedation Medication	Untreated (n = 15)		Treated (n = 15)		p value
	Number of Patients	Median (IQR)	Number of Patients	Median (IQR)	
Total lorazepam equivalent, mg/kg ^{21,22}	2	1.62 (0.25–2.99)	12	1.93 (0.48–6.93)	0.66
Total morphine equivalent, mg/kg ^{23–25}	3	18.18 (2.4–20.91)	13	13.06 (11.25–39.03)	0.90
Dexmedetomidine, mcg/kg	2	44.08 (5.5–82.67)	13	54.83 (24.47–188.20)	0.57

which also found no evidence of haloperidol reducing duration of delirium compared to placebo.^{39,40} Lastly, a 2018 Cochrane review article concluded that based on available studies antipsychotics do not reduce the severity of delirium or resolve symptoms compared to non-antipsychotic drugs or placebo.⁴¹ It is important to note that the overall quality of the data was rated as poor highlighting the need for additional controlled trials with well-defined outcome measures. Likewise, current pediatric delirium research is also limited to existing case reports, retrospective, and prospective studies without RCTs comparing pharmacologic treatment of pediatric delirium.

Traube et al⁴² suggested 3 classification systems of delirium: by type, time to event, and duration. Pediatric patients with delirium in our study developed all subtypes (hypoactive, hyperactive, and mixed), but we did not find differences between patients requiring antipsychotic treatment versus those who did not. This may be due to our small sample size.

The results also demonstrated that many children developed early-onset delirium in the course of the hospitalization, as opposed to a cohort who developed delirium later. About 50% of our treated patients developed delirium early and were effectively managed with a short course of antipsychotic treatment. Those who developed late-onset delirium had a longer, protracted course of delirium and required a longer duration of treatment. This raises an important question regarding duration of treatment, as there is paucity of research to assist in determining optimal treatment duration. The judicious use of antipsychotics includes using them for the shortest duration necessary to minimize potential adverse effects. Agar et al³⁷ suggested that in adult delirium, an intervention for symptom relief with no effect on symptoms in 72 hours is unlikely to be of benefit.

In our experience, patients who require antipsychotic treatment for early-onset delirium seem to respond quickly to antipsychotic treatment, whereas those treated for late-onset delirium have limited response to the antipsychotic treatment. Suboptimal response to late-onset delirium suggests there are confounding factors influencing a longer duration and severity of delirium and may include new comorbidities, increasing medical complexity, and tolerance to sedation and analgesic medications.

There are several limitations to this study. Although all patients were managed using a standard approach to assessment, diagnosis, and treatment of delirium, the sample size was likely too small to detect a difference between medications (e.g., sedatives, opioids) that may be risk factors for delirium. The data were from a single-center, large quality improvement project and may not be generalizable to other settings. Lastly, this was a retrospective secondary analysis study, which can introduce selection bias and information bias.

Conclusions

Antipsychotic use for the treatment of delirium in critically ill children who are refractory to non-pharmacologic measures was not associated with adverse events in the presence of appropriate comprehensive monitoring. Patients with early-onset delirium refractory to non-pharmacologic treatment may have a more effective response to antipsychotic therapy than may patients with late-onset refractory delirium. Further large-scale investigation is needed for differentiation of delirium subtypes/classification and identification of patients most likely to benefit from antipsychotics, with further development of treatment protocols to guide dose titration and treatment duration.

Table 5. Distribution of Sedation Medications for Patients After Screening Positive for Delirium

Sedation Medication	Untreated (n = 15)		Treated (n = 15)		p value
	Number of Patients	Median (IQR)	Number of Patients	Median (IQR)	
Total lorazepam equivalent, mg/kg ^{21,22}	9	0.41 (0.11–0.95)	13	3.83 (1.30–11.54)	0.071
Total morphine equivalent, mg/kg ^{23–25}	7	24.59 (9.0–36.69)	13	56.14 (16.16–63.11)	0.35
Dexmedetomidine, mcg/kg	4	171.80 (61.95–237.38)	14	125.0 (70.98–376.8)	0.72
Clonidine, mcg/kg	0	NA	3	0.0094 (0.0083–0.29)	n/a

NA, not applicable

ARTICLE INFORMATION

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