JPPT | PPA Membership Survey

Delirium Assessment Treatment Strategies in Critically Ill Pediatric Patients: A Pediatric Pharmacy Association Practice-Based Research Network Survey Study

Caitlyn V. Bradford, PharmD; Mon-Yee Fung, PharmD; Alexander Wang, PharmD; Emily C. Benefield, PharmD; Ferras Bashqoy, PharmD; Stephen B. Neely, MPH; and Peter N. Johnson, PharmD

OBJECTIVES The purpose of this study was to describe overall screening, prevention, and treatments for pediatric delirium at various neonatal intensive care units (NICUs), cardiac intensive care units (CICUs), and pediatric intensive care units (PICUs) from the Pediatric Pharmacy Association (PPA) membership. The primary objective was to identify the number of respondents that had a defined delirium-based protocol. The secondary objectives included identification of delirium assessment tools used, first- and second-line delirium treatment options, and monitoring practices for antipsychotics for delirium management.

METHODS A cross-sectional questionnaire was distributed to PPA members from February 8, 2022, to March, 25, 2022. Comparisons between the NICUs, PICUs, and CICUs were conducted by using chi-square tests, with *a priori* p value of <0.05

RESULTS The questionnaire was completed by 84 respondents at 62 institutions; respondents practiced in the PICU or mixed PICU (n = 48; 57.1%), CICU (n = 13; 15.5%), and NICU (n = 23; 27.4%). Sixty-one respondents (72.6%) noted their units routinely screen for delirium, and there was a significant difference between the respondents of different units that use a delirium scoring tool ($p < 0.01$). Only 33 respondents (39.3%) had a defined delirium protocol, and there was no difference between units ($p = 0.31$). The most common agents used for delirium treatment were quetiapine and risperidone. There was variability in the monitoring used between respondents, but the majority (n = 74; 88%) monitor electrocardiograms to assess the corrected QT interval, but practice variability existed.

CONCLUSIONS Most respondents did not have a defined delirium protocol. Variations were noted in the treatment options and monitoring for critically ill pediatric patients with delirium.

ABBREVIATIONS CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; CAPD, Cornell Assessment of Pediatric Delirium; CICU, cardiac intensive care unit; EKG, electrocardiogram ICU, intensive care unit; NICU, neonatal intensive care unit; PANDEM, pain, agitation, neuromuscular blockade and delirium; PBRN, Pharmacy Practice-Based Research Network; pCAM-ICU, pediatric Confusion Assessment Method for the Intensive Care Unit; PICU, pediatric intensive care unit; PPA, Pediatric Pharmacy Association; psCAM-ICU, Preschool Confusion Assessment Method for the Intensive Care Unit; SGA, second-generation antipsychotics

KEYWORDS critical care; delirium treatment; pediatric delirium

J Pediatr Pharmacol Ther 2023;28(6):540–552

DOI: 10.5863/1551-6776-28.6.540

Introduction

Delirium is defined as a sudden decreased attention, awareness, and cognition in critically ill patients, which can be classified as hyperactive, hypoactive, and mixed-types. While a temporary diagnosis, delirium is associated with poor outcomes including increased length of stay, longer duration of mechanical ventilation, morbidity, and mortality.[1] In adults, screening for delirium was initially dependent on psychiatry consults.[2,3] However, for the last 20 years, clinicians have routinely used validated tools for screening delirium, including the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).[1] However, in pediatric patients, tools for delirium assessment including the pediatric Confusion Assessment Method for the Intensive Care Unit (pCAM-ICU), Preschool Confusion Assessment Method for the Intensive Care Unit (psCAM-ICU), and Cornell Assessment of Pediatric Delirium (CAPD) were not validated until 10 to 15 years after implementation of the CAM-ICU.[4–7] As a result, there are limited data

on the epidemiology and effect of delirium in children, with the reported risk of pediatric delirium ranging from 12% to 65% depending on the critical care setting.[7,8] Recently, the 2022 Society of Critical Care Medicine's pain, agitation, neuromuscular blockade and delirium (PANDEM) guidelines include recommendations for routine delirium screening in critically ill children with the use of either pCAM-ICU, psCAM-ICU, or CAPD.[9]

Given the limited data pertaining to the epidemiology of delirium in critically ill pediatric patients, there is limited evidence for prevention and treatment strategies. The PANDEM guidelines suggest using non-pharmacologic strategies for delirium prevention, including good sleep hygiene, family engagement with patient care, and early mobilization.[9] In addition, they provide pharmacologic recommendations for prevention and treatment, including minimizing sedation and removal of agents that may increase the risk of delirium. The PANDEM guidelines also provide limited recommendations for use of antipsychotics with recommendations against the routine use of antipsychotics for prevention or treatment of delirium. However, they suggest haloperidol or second-generation antipsychotics (SGAs) could be used for refractory, severe delirium management, but the guidelines do not specify a specific antipsychotic of choice. Commonly reported agents used to treat pediatric delirium include haloperidol and SGAs including quetiapine, olanzapine, and risperidone.[7,9] These medications do not currently have US Food and Drug Administration–labeled indications for the prevention or treatment of pediatric delirium. Therefore, the selection of these agents is based on provider preference, adverse event consideration, and available dosage forms of these agents. The PANDEM guidelines provide minimal recommendations for consideration of antipsychotic adverse events with the recommendation of baseline electrocardiogram (EKG) and electrolyte monitoring to assess the potential of a QTc interval. However, the guidelines provide no recommendations on other antipsychotic adverse events including metabolic syndrome, extrapyramidal symptoms, sedation, and potential future neurodevelopmental effects.[9,10]

Given the lack of consensus on prevention or treatment options for pediatric delirium, there is likely a wide variety of practices across health-systems caring for critically ill pediatric patients. Some institutions may not have a specific protocol in place for screening, prevention, and treatment given the fact that the PANDEM guideline recommendations have only recently been published. Alternatively, other health-systems may have created their own guidelines that may vary from other institutions and also within different intensive care units (ICUs) within the same health-systems. The purpose of this study was to characterize delirium screening, prevention, and pharmacotherapeutic strategies used in health-systems with neonatal intensive care units (NICUs), cardiac intensive care units (CICUs), and/or pediatric intensive care units (PICUs).

Materials and Methods

Study Design and Survey Administration. This was a descriptive survey study of pediatric clinical pharmacists. The survey included 484 questions including health-system demographics, delirium screening practices, non-pharmacologic prevention strategies, and pharmacologic prevention and treatment therapies. The survey used cascading questions and branching logic based on answers to previous questions. Questions consisted of multichoice, rank order, text entry, and mark all that apply, and the questionnaire required a forced response for each question. Even though the questionnaire included 484 questions, the length was dependent on whether the management of delirium was based on delirium subtypes (i.e., hyperactive, mixed, hypoactive), the different antipsychotics used, and the types of adverse events monitored with antipsychotics. A summary of these questions is included in the Supplemental Table.

The electronic questionnaire was developed and distributed via Qualtrics (Provo, UT) via email through the Pediatric Pharmacy Association's (PPA's) Pharmacy Practice-Based Research Network (PBRN) from February 8 to March 25, 2022, with 2 reminder emails sent within this period. Members of PPA were able to forward the link to the questionnaire to nonmembers at their institution for increased participation. Based on information provided by the PPA Interim Executive Director in March 2022, there were approximately 957 pharmacist members representing 310 health-systems, which included 268 NICUs (86.5%), 178 PICUs (57.4%), and 70 CICUs (22.6%). Clinicians were asked to provide their institution and practice site area to ensure that results were not duplicated. Participation in the survey was voluntary and anonymous. Incomplete surveys were excluded from analysis.

Study Objectives and Data Analysis. Demographic data collected included the institution, specific area of practice, and number of beds per unit. Regarding information on clinical practices, the data collected consisted of identification of internal delirium protocol (if applicable) for the specific ICU, delirium scoring system used (if applicable), the frequency of delirium scoring, delirium preventative measures, and adjunctive therapy use. Regarding delirium pharmacotherapy, the data collected included the medications used, ranking of medication from most to least frequently used, dosing (mg or mg/kg), dosage formulation, frequency of dosing, adverse effect monitoring (e.g., dyslipidemia, hyperprolactinemia, hypertriglyceridemia, QTc prolongation), and titration and tapering strategies.

The primary objective was to identify the number of respondents that had a defined delirium-based

protocol. The secondary objectives included identification of delirium assessment tools used, non-pharmacologic and pharmacologic options for delirium prevention, first- and second-line delirium treatment options, and monitoring practices for antipsychotics for delirium management. For the first- and second-line delirium treatment options, respondents were asked to specify the treatment options based on delirium subtypes (if applicable). An additional secondary objective included comparing differences in delirium assessment practices, melatonin use for delirium prevention, and delirium treatment protocols between the NICU, PICU, and CICU settings.

To ensure face validity of the survey instrument, the questionnaire was developed and reviewed by all investigators. In addition, informal feedback was obtained from 3 pediatric pharmacists who serve on the PPA PBRN and 3 clinical pharmacy specialists, unaffiliated with the PPA PBRN. Descriptive statistics including frequencies and percentages were used to summarize the survey responses. Comparisons between the NICU, PICU, and CICU were conducted by using chi-square tests, using SAS version 9.4 (SAS Institute Inc, Cary, NC), with *a priori* p value of <0.05.

Results

Demographics. During the study period, 84 surveys were completed and included in analysis, representing 62 health-systems. A single respondent was identified from 44 different health-systems, 2 respondents in 2 different ICUs from 12 health-systems, and 3 respondents from 3 different ICUs from 6 health-systems. An overall response rate of 20% was calculated from the 310 health-systems represented by PPA members.

General background and demographics of the institutions with completed surveys can be found in Table 1. Most respondents (n = 33; 39.3%) were from the Southeast. Most institutions of respondents (n = 65; 77.4%) had between 0 and 50 beds in their units. Most respondents (n = 48; 57.1%) practiced in the PICU or a mixed PICU, which respondents defined as a PICU that took care of medical and cardiac patients. The remaining respondents practiced in the NICU (n = 23; 27.4%) or CICU (n = 13; 15.5%). For respondents who practiced in the NICU, there was variability in the type of rooms available, with the majority (n = 12; 52.2%) practicing in a NICU that had both patient-specific and open-air rooms.

Delirium Screening Practices, Protocols, and Prevention Strategies. There was variability in the use of delirium scoring tools between respondents. Sixty-one respondents (72.6%) used a delirium scoring tool to assess patients. There was a significant difference with the use of scoring tools between the respondents, based on practice setting (p < 0.01), with respondents from the NICU setting reporting the lowest use of delirium scoring tools (n = 11; 47.8%). Of the 61 respondents who use delirium scoring tools, the most common scoring tool reported was the CAPD score (n = 54; 88.5%). Respondents noted that most providers (n = 43; 70.5%) performed delirium screening every shift (i.e., 8–12 hours).

Table 2 provides the results of non-pharmacologic and pharmacologic delirium prevention strategies. Most institutions used a wide variety of non-pharmacologic delirium prevention strategies discussed in the PANDEM guidelines, including family member involvement and early mobilization.

However, only 26 respondents (31.0%) noted that their units used noise-reducing devices such as earplugs or headphones. In terms of pharmacologic prevention strategies, most respondents (n = 64; 76.2%) noted that their units limit the use of benzodiazepines and used light sedation. Thirty-six respondents (42.4%) used melatonin as a preventive strategy for delirium, with 8 of 13 respondents (61.5%) from the CICU who noted the highest usage of melatonin. However, there was no significant difference in those who used melatonin between units (p = 0.33).

Thirty-three respondents (39.3%) noted their unit had a delirium treatment protocol. There was no significant difference in those with treatment protocols between the respondents, based on practice setting (p = 0.31). Only 21 respondents (25.0%) noted that they required a psychiatry consult prior to initiation of antipsychotics.

Delirium Treatment Options. Respondents were asked for the first- and second-line treatment options that they used at their institution to treat delirium. For the 51 respondents without a delirium protocol, they noted that they did not differentiate their treatment options based on delirium subtype. Among the 33 respondents whose ICU had a delirium treatment protocol, there were 9 respondents who had specific recommendations for delirium treatment, based on the delirium subtype. Seven of these (21.3%) had different treatment options for patients with hyperactive, hypoactive, and mixed delirium. One respondent (3.0%) had delirium treatment options for patients with hyperactive delirium only. An additional 1 respondent (3.0%) had treatment options for patients who had hyperactive and hypoactive delirium. The remaining 24 respondents (n = 72.7%) with a delirium protocol only had general treatment options that were not specific for delirium subtype. Given all of the different delirium subtypes for the different ICU units, there were 99 overall responses for the CICU (n = 15), PICU or mixed PICU (n = 55), and NICU (n = 29) regarding the first- and second-line treatment options.

Table 3 provides a description of first- and second-line delirium treatment options based on the ICU unit and delirium subtype. There was variability in agents used for delirium, but first and SGAs (n = 87; 87.9%) were the most common first-line option. The 2 most common first-line agents were quetiapine (n = 35; 35.4%) followed by risperidone (n = 32; 32.3%). For

Table 1. Baseline Demographics of Health-Systems for Respondents and Delirium Assessment

Variable	Overall (N = 84)	CICU (n = 13)	PICU/Mixed PICU (n = 48)	NICU (n = 23)
	No. (%)			
Location of institutions				
Northeast	14 (16.7)	2 (15.4)	7 (14.6)	5 (21.7)
Midwest	20 (23.8)	2 (15.4)	12 (25)	6 (26.1)
Southeast	33 (39.3)	6 (46.2)	18 (37.5)	9 (39.1)
West	17 (20.2)	3 (23.1)	11 (22.9)	3 (13.0)
Total bed size				
0–25	41 (48.8)	7 (53.8)	31 (64.5)	3 (13.0)
26–50	24 (28.6)	3 (23.1)	12 (25.0)	9 (39.1)
51–75	9 (10.7)	1 (7.7)	2 (4.2)	6 (26.1)
>75	10 (11.9)	2 (15.4)	3 (6.3)	5 (21.8)
Type of NICU rooms available in unit				
Patient-specific rooms	—	—	—	7 (30.4)
Open-air rooms	—	—	—	4 (17.4)
Both	—	—	—	12 (52.2)
Use a delirium screening tool*	61 (72.6)	9 (69.2)	41 (85.4)	11 (47.8)
Delirium screening tool used (n = 61)				
pCAM-ICU/psCAM-ICU	6 (9.9)	—	5 (8.3)	1 (1.6)
CAPD	54 (88.5)	9 (14.7)	35 (57.4)	10 (16.4)
Unsure	1 (1.6)	—	1 (1.6)	—
Frequency of delirium scoring (n = 61)				
Every 24 hr	3 (4.9)	—	1 (1.6)	2 (3.3)
Every shift (8 or 12 hr)	43 (70.5)	6 (9.9)	31 (50.7)	6 (9.9)
Other	8 (13.1)	3 (4.9)	5 (8.2)	—
Unsure	7 (11.5)	—	4 (6.6)	3 (4.9)

CAPD, Cornell Assessment of Pediatric Delirium; CICU, cardiac intensive care unit; NICU, neonatal intensive care unit; pCAM-ICU, pediatric Confusion Assessment Method for the Intensive Care Unit; PICU, pediatric intensive care unit; psCAM-ICU, Preschool Confusion Assessment Method for the Intensive Care Unit

*$p < 0.01$.

second-line agents, most were risperidone (n = 16, 16.2%) and quetiapine (n = 25; 25.3%). However, 37 respondents (37.4%) did not specify a particular agent that they used. It is important to note that there was more variability in the agents used first- and second-line for respondents whose ICU unit did not have a protocol. Some of the options used for these units included melatonin, chlorpromazine, and ziprasidone. In addition to this, respondents were asked about other alternative or adjunct agents that were used at their institutions. These included chloral hydrate (n = 1; 1.2%), clonidine or dexmedetomidine (n = 57; 67.9%), gabapentin (n = 40; 47.6%), ketamine (n = 22; 26.2%), and melatonin (n = 3; 3.6%).

Table 4 provides an overview of the melatonin and antipsychotic treatment regimens used by respondents. Most of the 36 respondents who reported use of melatonin (n = 23; 63.9%) use fixed-dosing administered at night. There was variability in the dosage formulations available for melatonin, with most using tablets or capsules (n = 33; 91.7%). For the 18 respondents who used haloperidol, the majority (n = 13; 72.2%) used weight-based dosing and administered on an as-needed basis rather than scheduled dosing (n = 12; 66.6%). There were 56 respondents who used quetiapine as a first- or second-line treatment option. Most used weight-based dosing (n = 29; 51.8%) at variable frequencies, including every 8 to 24 hours. Fifty respondents noted that they use risperidone as a treatment option. The majority (n = 31; 62.0%) used fixed dosing and administer daily dosing (n = 46; 92.0%). There were 24 respondents who used olanzapine. Most used fixed dosing (n = 18; 75.0%) administered once daily (n = 21; 87.5%). For the antipsychotics, respondents were asked if they tapered the dosing before discontinuation. There was variability in the duration of taper with some using no taper and others using a 1- to 2-, 2- to 4-, or >4-week taper.

Adverse Event Monitoring for Antipsychotics. Table 5 provides an overview of adverse event monitoring with antipsychotics. Twenty-three respondents (27.4%) had a delirium protocol that included monitoring for adverse events. The most common adverse

Table 2. Delirium Prevention and Treatment Protocol Data

Variable	Unit-Wide Variables			
	Overall (N = 84)	CICU (n = 13)	PICU/Mixed PICU (n = 48)	NICU (n = 23)
	No. (%)			
Delirium Prevention Protocol Data				
Non-pharmacologic prevention strategies				
Child life involvement	67 (79.8)	12 (92.3)	44 (91.7)	11 (47.8)
Family member involvement	73 (86.9)	13 (100)	42 (87.5)	18 (78.3)
Supporting developmentally appropriate sleep-wake cycles	69 (82.1)	10 (76.9)	40 (83.3)	19 (82.6)
Avoid physical restraints	49 (58.3)	8 (61.5)	31 (64.6)	10 (43.5)
Early mobilization	51 (60.7)	5 (38.5)	38 (79.2)	8 (34.8)
"Hands-off" periods/clustering care to allow for uninterrupted sleep	54 (64.3)	10 (76.9)	27 (56.3)	17 (73.9)
Noise-reducing devices (e.g., headphones, earplugs)	26 (31.0)	4 (30.8)	15 (31.3)	7 (30.4)
Scheduled lab tests outside of designated sleeping hours	19 (22.6)	6 (46.2)	11 (22.9)	2 (8.7)
Pharmacologic prevention strategies				
Limitation of benzodiazepines	64 (76.2)	11 (84.6)	36 (75.0)	17 (73.9)
Using light sedation	64 (76.2)	8 (61.5)	37 (77.1)	19 (82.6)
Discontinuing anticholinergics	30 (35.7)	6 (46.2)	20 (41.7)	4 (17.4)
Preventative melatonin*	36 (42.4)	8 (61.5)	19 (39.6)	9 (39.1)
Delirium Treatment Protocol Data				
Treatment protocol overview				
Protocol in place for ICUs†	33 (39.3)	6 (46.2)	21 (43.8)	6 (26.1)
Required psychiatry consultant prior to antipsychotic use	21 (25.0)	1 (7.7)	16 (33.3)	4 (17.4)

CICU, cardiac intensive care unit; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit

*p = 0.33.
†p = 0.31.

event monitored was assessment of QTc prolongation (n = 74; 88.1%). Most respondents (n = 61; 82.4%) indicated that a baseline EKG was routinely obtained. There was variability in the frequency of electrolyte assessment in conjunction with EKG for assessment of QTc prolongation. Respondents were asked if the number of concomitant QTc-prolonging medications affected the decision to initiate an antipsychotic; however, most (n = 54; 73.0%) specified that they did not have a threshold of concomitant agents before initiation of QTc-prolonging antipsychotics. In addition, there was variability in frequency of EKG assessment with some who monitored daily, weekly, or another frequency not defined. The majority (n = 50; 67.6%) indicated a threshold to discontinue antipsychotics with most (n = 33; 66.0%) who noted a QTc >500 msec would precipitate antipsychotic discontinuation.

Respondents were also asked if they monitored for hypertriglyceridemia and hyperprolactinemia with antipsychotics. Twenty-six (31.0%) monitored for hypertriglyceridemia, but there was variability in the frequency of monitoring triglycerides. In addition, most respondents did not have a threshold for triglycerides in which they would discontinue antipsychotics. Five respondents (6.0%) noted that their providers monitored for signs of hyperprolactinemia.

Discussion

Five previous survey studies have been published describing delirium screening and prevention and treatment practices in the PICU setting in the United States and internationally.[11–15] However, to our knowledge, this is the first study that describes delirium screening, prevention, treatment, and monitoring practices in NICU, PICU, and CICUs. Only one of these studies reported on the use of a delirium screening and treatment protocol. Aljabari and colleagues[11] conducted a survey of 42 of 71 PICU fellowship directors (59% response rate) to explore characteristics of delirium screening and treatment in their institutions, and they noted 23 (54.8%) had a delirium protocol. Our survey was targeted at pediatric pharmacists at PPA institutions. We noted a

Table 3. First- and Second-Line Delirium Treatments Arranged by ICU Unit and Type of Delirium Subtype Treated

Variable	Overall (N = 99)			CICU			PICU/Mixed PICU			NICU		
	All (n = 99)	Protocol (n = 42)	Non-Protocol (n = 57)	All (n = 15)	Protocol (n = 6)	Non-Protocol (n = 9)	All (n = 55)	Protocol (n = 26)	Non-Protocol (n = 29)	All (n = 29)	Protocol (n = 10)	Non-Protocol (n = 19)
First-line agent used												
Chlorpromazine	1 (1)	—	1 (1.8)	1 (6.7)	—	1 (11.1)	—	—	—	—	—	—
Haloperidol	2 (2)	1 (2.4)	1 (1.8)	—	—	—	1 (1.8)	1 (3.8)	—	1 (3.4)	—	1 (5.3)
Melatonin	1 (1)	—	1 (1.8)	—	—	—	1 (1.8)	—	1 (3.4)	—	—	—
Olanzapine	17 (17.2)	7 (16.7)	10 (17.5)	1 (6.7)	—	1 (11.1)	11 (20.0)	4 (15.4)	7 (24.1)	5 (17.2)	3 (30)	2 (10.5)
Quetiapine	35 (35.4)	17 (40.5)	18 (31.6)	5 (33.3)	3 (50.0)	2 (22.2)	20 (36.4)	10 (38.5)	10 (34.5)	10 (34.5)	4 (40)	6 (31.6)
Risperidone	32 (32.3)	17 (40.5)	15 (26.3)	8 (53.3)	3 (50.0)	5 (55.6)	17 (30.9)	11 (42.3)	6 (20.7)	7 (24.1)	3 (30)	4 (21.1)
No treatment specified	11 (11.1)	—	11 (19.3)	—	—	—	5 (9.1)	—	5 (17.2)	6 (20.7)	—	6 (31.6)
Second-line agent used												
Haloperidol	11 (11.1)	5 (11.9)	6 (10.5)	4 (26.7)	—	4 (44.4)	5 (9.1)	3 (11.5)	2 (6.9)	2 (6.9)	2 (20)	—
Melatonin	2 (2.0)	—	2 (3.5)	—	—	—	1 (1.8)	—	1 (3.4)	1 (3.4)	—	1 (5.3)
Olanzapine	6 (6.1)	3 (7.1)	3 (5.3)	3 (20.0)	1 (16.7)	2 (22.2)	3 (5.5)	2 (7.7)	1 (3.4)	—	—	—
Quetiapine	25 (25.3)	11 (26.2)	14 (24.6)	4 (26.7)	2 (33.3)	2 (22.2)	16 (29.1)	7 (26.9)	9 (31)	5 (17.2)	2 (20)	3 (15.8)
Risperidone	16 (16.2)	10 (23.8)	6 (10.5)	1 (6.7)	1 (16.7)	—	12 (21.8)	8 (30.8)	4 (13.8)	3 (10.3)	1 (10)	2 (10.5)
Trazadone	1 (1.0)	1 (2.4)	—	—	—	—	1 (1.8)	1 (3.8)	—	—	—	—
Ziprasidone	1 (1.0)	—	1 (1.8)	—	—	—	—	—	—	1 (3.4)	—	1 (5.3)
No treatment specified	37 (37.4)	12 (28.6)	25 (43.9)	3 (20.0)	2 (33.3)	1 (11.1)	17 (30.9)	5 (19.2)	12 (41.4)	17 (58.6)	5 (50)	12 (63.2)

CICU, cardiac intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit

Table 4. Overview of Melatonin and Antipsychotic Treatment Regimens Used

Variable	No. (%) or Median (IQR)
Melatonin (n = 36)	
Type of dosing	
Weight-based dosing	4 (11.1)*
Fixed dosing	23 (63.9)†
No standard dosing used	9 (25.0)
Dosing frequency	
Daily dosing (at night)	36 (100)
Dosage forms used	
Commercially available oral solution/suspension	18 (50)
Gummies	—
Oral disintegrating tablet	1 (2.8)
Tablets/capsules	33 (91.7)
Antipsychotics	
Haloperidol (n = 18)	
Dosage forms used	
Commercially available oral solution/suspension	4 (22.2)
Intramuscular	13 (72.2)
Intravenous solution	14 (77.8)
Tables/capsules	9 (50)
Type of dosing	
Weight-based dosing‡	13 (72.2)
Fixed dosing§	2 (11.1)
No standard dosing used	3 (16.7)
Dosing frequency	
Every 8–12 hr dosing	6 (33.4)
As-needed dosing	12 (66.6)
Frequency of titration	
<24 hr	1 (5.6)
24–48 hr	4 (22.2)
>48 hr	1 (5.6)
Not applicable (not given for maintenance dosing)	12 (66.6)
Duration of taper	
No taper	1 (5.6)
1–2 wk	4 (22.2)
2–4 wk	1 (5.6)
Not applicable (not given for maintenance dosing)	12 (66.6)
Risperidone (n = 50)	
Dosage forms used	
Commercially available oral solution/suspension	44 (88.0)
Intramuscular	1 (2.0)
Orally disintegrating tablets	13 (26.0)
Tables/capsules	34 (68.0)
Type of dosing	
Weight-based dosing¶	12 (24.0)
Fixed dosing#	31 (62.0)
No standard dosing used	7 (14.0)
Dosing frequency	
Daily dosing	46 (92.0)
Every 12–24-hr dosing	4 (8.0)

Table 4. Overview of Melatonin and Antipsychotic Treatment Regimens Used *(cont.)*

Variable	No. (%) or Median (IQR)
Frequency of titration	
<24 hr	2 (4.0)
24–48 hr	23 (46.0)
>48 hr	16 (32.0)
Not specified	9 (18.0)
Duration of taper	
No taper	13 (26.0)
1–2 wk	6 (12.0)
2–4 wk	15 (30.0)
>4 wk	16 (32.0)
Olanzapine (n = 24)	
Dosage forms used	
Commercially available oral solution/suspension	4 (16.7)
Intramuscular	8 (33.3)
Orally disintegrating tablets	18 (75.0)
Tables/capsules	20 (83.3)
Type of dosing	
Weight-based dosing**	3 (12.5)
Fixed dosing††	18 (75.0)
No standard dosing used	3 (12.5)
Dosing frequency	
Daily dosing	21 (87.5)
Every 12–24-hr dosing	3 (12.5)
Frequency of titration	
<24 hr	5 (20.8)
24–48 hr	2 (8.3)
>48 hr	13 (54.2)
Not specified	4 (16.7)
Duration of taper	
No taper	5 (20.8)
1–2 wk	5 (20.8)
2–4 wk	9 (37.6)
>4 wk	5 (20.8)
Quetiapine (n = 56)	
Dosage forms used	
Commercially available oral solution/suspension	33 (58.9)
Tables/capsules	49 (87.5)
Type of dosing	
Weight-based dosing‡‡	29 (51.8)
Fixed dosing§§	23 (41.1)
No standard dosing used	4 (7.1)
Dosing frequency	
Daily dosing	4 (7.1)
Every-12-hr dosing	4 (7.1)
Every-8-hr dosing	16 (28.7)
Frequency not specified	32 (57.1)
Frequency of titration	
<24 hr	1 (1.8)
24–48 hr	39 (69.6)
>48 hr	8 (14.3)
Not specified	8 (14.3)

(Table cont. on page 548)

Table 4. Overview of Melatonin and Antipsychotic Treatment Regimens Used *(cont.)*

Variable	No. (%) or Median (IQR)
Duration of taper	
No taper	14 (25.0)
1–2 wk	9 (16.1)
2–4 wk	17 (30.4)
>4 wk	16 (28.5)

*Weight-based dosing included 0.05 mg/kg/dose (n = 2) and 0.1 mg/kg/dose (n = 2).
†Fixed dosing included 0.5 to 1 mg/dose (n = 9), 1.5 to 3 mg/dose (n = 4), 3 mg/dose (n = 4), and dosing dependent upon age and/or weight (n = 6).
‡Weight-based dosing included 0.01 to 0.075 mg/kg/dose (n = 9), 0.1 mg/kg/dose (n = 2), 0.15 to 0.25 mg/kg/dose (n = 2).
§Fixed dosing based on age.
¶Weight-based dosing included 0.01 to 0.025 mg/kg/dose.
#Fixed dosing included 0.05 to 0.1 mg/dose (n = 6), >0.1 to 0.25 mg/dose (n = 8), and dosing dependent upon age and/or weight (n = 17).
**Weight-based dosing included 0.1 mg/kg/dose.
††Fixed dosing included 0.625 to 2.5 mg (n = 3) and dosing dependent upon age and/or weight, ranging from 0.625 to 5 mg/dose (n = 15).
‡‡Weight-based dosing included 0.5 mg/kg/dose daily to every 8 hours.
§§Fixed dosing included dosing dependent upon age and/or weight, ranging from 6.25 to 50 mg/dose daily to every 8 hours.

slightly lower number of respondents (n = 33; 39.3%) than Aljabari and colleagues.[11] One possible difference in these findings was that our survey also included CICU and NICU units. While we found no difference between units in those that had a protocol (p = 0.31), we found only 26% of NICU respondents who have an established delirium protocol. This may be because there are still a number of unanswered questions that currently exist in terms of screening and risk factors in the neonatal population.[9]

In our study, we noted 61 respondents (72.6%) who routinely use delirium screening. For the other survey studies that have evaluated delirium management practices, the range of institutions using a delirium screening tool has ranged from 0% to 60%.[11–15] Most respondents (n = 54; 88.5%) who conducted a delirium assessment noted that the CAPD was the most common delirium screening tool. These findings are similar to 4 other studies that reported on the type of delirium screening tools used in the PICU setting, where they also noted the CAPD as the most common screening tool.[11,12,14,15] In our study, we also noted variability on the frequency of delirium scoring, with most respondents indicating that this was conducted every shift (e.g., 8 or 12 hours). One reason for the variability in the frequency in which delirium screening was used may be due to inconsistencies in recommendations in the literature. The 2016 European Society of Paediatric and Neonatal Intensive Care position statement on pain, sedation, withdrawal, and delirium assessment recommends that delirium screening be used every 8 to 12 hours.[8] The PANDEM guidelines do recommend routine delirium screening.[9] However, they do not provide a specific recommendation on how many times a day the scoring should be conducted.

Respondents in our survey noted a variety of non-pharmacologic and pharmacologic preventative measures for delirium. Most respondents in our study noted that they routinely engage family members and child life specialists in the care of children in their units and use early mobilization strategies. In addition, 82% of respondents noted that they support developmentally appropriate promotion of sleep-wake cycles including light reduction to prevent delirium and aid in sleep promotion. However, we noted only one-third of respondents use noise-reducing devices. Of the 5 previous survey studies describing delirium practices in PICUs, only 3 reported on non-pharmacologic prevention practices on sleep promotion and delirium prevention.[12–14] These studies noted significant variability in non-pharmacologic prevention strategies like light reduction and sleep promotion strategies (9%–83%) and noise-reducing devices (0%–22%). The PANDEM guidelines provide a number of recommendations on sleep promotion and delirium prevention, including interdisciplinary rounds, family involvement, early mobility, and sleep hygiene (e.g., light reduction and implementation of noise-reducing devices). Based on these studies and our survey, it is clear that there is a need to further optimize some of these non-pharmacologic strategies. Our data highlight an opportunity for pediatric pharmacists to work with the interdisciplinary NICU, PICU, and CICU teams to ensure that these non-pharmacologic therapies are implemented.

Our survey also noted a few pharmacologic prevention strategies used. Approximately three-quarters of respondents noted that their units use light sedation and limit the use of benzodiazepines. However, only 35% of respondents noted that they routinely discontinue anticholinergics. The PANDEM guidelines recommend analgosedation regimens with light sedation and minimizing the use of benzodiazepine-based sedation regimens, because benzodiazepines have been independently associated with the development of delirium in critically ill children.[9,16] It should be noted that the PANDEM guidelines do not give specific recommendations on the use of anticholinergics. Various studies have noted conflicting findings on the effect

Table 5. Adverse Event Monitoring Components of Antipsychotics by Respondents

Variable	No. (%) or Median (IQR)
Standardized adverse event protocol (n = 84)	
Yes	23 (27.4)
No	48 (57.1)
Unsure	13 (15.5)
Adverse events monitored (n = 84)	
Hyperprolactinemia	5 (6.0)
Hypertriglyceridemia	26 (31.0)
QTc prolongation	74 (88.1)
Dyslipidemia	
Frequency of monitoring for hypertriglyceridemia (n = 26)	
Daily	1 (3.8)
Weekly	12 (46.2)
Monthly	5 (19.2)
Other	8 (30.8)
Established threshold of triglycerides to discontinue antipsychotics (n = 26)	
Yes	11 (42.3)
Not established	15 (57.7)
Triglyceride threshold (n = 11)	
>250 mg/dL	4 (36.4)
>300–400 mg/dL	2 (18.1)
>500 mg/dL	5 (45.5)
Hyperprolactinemia	
Frequency of monitoring for hyperprolactinemia (n = 5)	
Monthly	2 (40.0)
Weekly	2 (40.0)
Other	1 (20.0)
Cardiac Toxicity	
Baseline EKG performed (n = 74)	
Yes	61 (82.4)
No	13 (17.6)
Electrolyte monitoring at baseline in conjunction with EKG (n = 74)	
Yes	54 (73.0)
No	20 (27.0)
Frequency of EKG monitoring (n = 74)	
Daily	5 (6.8)
Weekly	30 (40.5)
Other	39 (52.7)
Amount of concomitant QTc-prolonging agents affect selection of antipsychotics treatment (n = 74)	
Not specified	54 (73.0)
≥1	2 (2.7)
≥2	8 (10.8)
≥3	8 (10.8)
≥4	2 (2.7)
Frequency of electrolyte monitoring while on antipsychotics (n = 74)	
Daily	24 (32.4)
Twice weekly	10 (13.5)
Weekly	10 (13.5)
Not specified	30 (40.6)

EKG, electrocardiogram

of anticholinergics in critically ill children.[17–19] We also noted approximately 40% of respondents use melatonin as a prevention strategy for delirium. In critically ill adults, some studies have noted melatonin may decrease the risk of delirium.[20] To our knowledge, only 2 studies have evaluated the use of melatonin in critically ill children in the PICU, NICU, or CICU.[21,22] These studies were limited in that they were retrospective and included a total of 118 children. However, they noted a reduction in sedation scores and cumulative dosing of opioids and thus could be associated with a potential role in prevention of delirium.[21,22] Despite these findings, the 2022 PANDEM guidelines provide no specific recommendations on the role of melatonin owing to the lack of quality data.[9]

Our survey explored the first- and second-line treatment options of respondents. Seven respondents (21.3%) had a delirium protocol that had specific recommendations based on delirium subtypes (i.e., hyperactive, hypoactive, and mixed). Given all of the delirium subtypes for the different units, 99 responses were collected for the first- and second-line delirium treatments for the CICU, PICU or mixed PICU, and NICU. Most respondents (88%) noted SGAs were the most common first-line treatment option, and a variety of different dosage regimens and dosage forms were used amongst the respondents. The most common first- and second-line agents used were quetiapine and risperidone. The PANDEM guidelines suggest that haloperidol or SGAs can be used for refractory delirium, but do not provide a specific recommendation of one agent over another. To our knowledge, 17 reports have evaluated the use of haloperidol, olanzapine, quetiapine, or risperidone in a total of 481 children.[23–39] While these reports provide some preliminary data, they are limited in that they were retrospective, did not assess consistent outcomes, and used different dosage regimens. Most of the more recent studies have evaluated the use of risperidone or quetiapine, which may have been why these were the 2 most common agents used by respondents in our study.[25,29,32–39] It should be noted that some respondents used non-antipsychotics as a first- or second-line therapy or adjunct agent for delirium, including melatonin, chloral hydrate, clonidine, or gabapentin. To date, no studies in critically ill children have explored the use of these agents to decrease delirium, and none of these agents are mentioned as treatment options in the PANDEM guidelines.[9]

Respondents were also asked a variety of questions regarding monitoring parameters for antipsychotics for children with delirium in their units. Only one-third of respondents had a section of their delirium protocol that provided recommendations for monitoring adverse events. The majority (88%) monitored EKGs in the setting of antipsychotic therapy. The PANDEM guidelines recommend a baseline EKG and routine electrolyte and QTc monitoring.[9] However, they do not provide any specific recommendations on the frequency of EKG monitoring or the threshold for discontinuing or adjusting antipsychotics, based on the QTc. Most respondents (82%) did collect a baseline EKG, but there was considerable variability on the frequency of EKGs and electrolyte assessment after initiation of therapy. In addition, most indicated that they used a QTc threshold of >500 msec. Other sources have recommended that antipsychotics be discontinued or decreased in patients with a QTc >450 msec or a 25% increase from baseline.[10] However, it may be difficult to make definitive recommendations for all pediatric patients, and thus consideration of risk factors and other concomitant medications should be considered.

In addition to considerations for QTc monitoring, one-third of respondents monitor for hypertriglyceridemia. These findings are similar to that of Aljabari and colleagues[11] who noted only 10% of respondents assessed triglycerides in patients receiving antipsychotics. It should be noted that the PANDEM guidelines do not provide recommendations for other adverse events associated with antipsychotics, including hypertriglyceridemia or hyperprolactinemia. However, it is well established that SGAs are associated with cardiometabolic toxicities after a treatment duration greater than 4 weeks.[10] A systematic review evaluating haloperidol and SGAs for delirium in critically ill children noted that the duration of antipsychotics ranged from 2 to 151 days.[10] Considering the possibility of these cardiometabolic effects in children with antipsychotics, the American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity recommended a fasting lipid panel, blood pressure, and plasma glucose test every 3 months after initiation of therapy.[40] We also noted 6% of respondents monitored for hyperprolactinemia. This adverse event has also been reported with antipsychotics, but there remain limited recommendations on the frequency of hyperprolactinemia in hospitalized children.[10]

This study had several limitations. First, the study included a small sample size. However, despite the small sample size, the survey included respondents from a mixture of units across the United States, including different bed sizes and geographic locations. In addition to this, our study is also unique in that it reports on a description of practices in the NICU and CICU. Second, our survey was disseminated before the publication of the 2022 PANDEM guidelines. Therefore, it is likely that some of the respondents would have implemented some of the recommended practices used in the guidelines for delirium. Third, psychometric data for the survey are limited, so there could have been confusion by some respondents with completing the questionnaire. However, face validity for our questionnaire was established by practicing pediatric pharmacists before the survey was disseminated.

Conclusion and Future Directions

This study found that a minority of respondents have a standardized delirium protocol for screening, prevention, and treatment in critically ill children. The majority (73%) use delirium screening and a number of non-pharmacologic prevention strategies. The minority of respondents (40%) use melatonin for prevention of delirium. For delirium treatment, most use antipsychotics, with quetiapine and risperidone among the most common agents. Variations were noted in monitoring practices for QTc prolongation, dyslipidemia, and hyperprolactinemia.

Until future studies are conducted that focus on delirium prevention and treatment in critically ill children, these findings may be used by pediatric clinical pharmacists to identify opportunities for quality improvement initiatives in their institutions. Pediatric clinical pharmacists should work with interprofessional teams in the NICU, PICU, and CICU to develop delirium prevention and treatment protocols. In addition, our findings indicate variability in the first-line antipsychotic for delirium. The results of our study can serve as a foundation for multicenter research through the PPA PBRN to explore the efficacy and safety of pharmacologic for critically ill children with delirium.

Article Information

Affiliations. Department of Pharmacy Practice (CVB), Philadelphia College of Pharmacy, Saint Joseph's University, Philadelphia, PA; Department of Pharmacy (M-YF), University of Michigan MOTT Children's Hospital, Ann Arbor, MI; Department of Pharmacy (AW), Children's National Hospital, Washington, DC; Department of Pharmacy (ECB), Seattle Children's Hospital, Seattle, WA; Department of Pharmacy (FB), Hassenfeld Children's Hospital at NYU Langone Health, New York City, NY; Department of Pharmacy: Clinical and Administrative Sciences (SBN, PNJ), College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Correspondence. Peter N. Johnson, PharmD; peter-johnson@ouhsc.edu

Disclosure. Three authors (ECB, FB, PNJ) are members of the PPA PBRN. Otherwise, the authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and has been approved by our institutional review board. Given the nature of this study, informed consent, assent, and parental permissions were not required.

Acknowledgment. At the time of this study Dr Bradford was a PGY2 Pediatric Pharmacy Resident at The University of Oklahoma College of Pharmacy, Dr Fung was a PGY2 Pediatric Pharmacy Resident at Primary Children's Hospital in Salt Lake City, Utah, and Dr Wang was a PGY2 Pediatric Pharmacy Resident at NYU Langone Health. The authors would like to acknowledge the PPA PBRN who helped review the study proposal and survey.

Submitted. November 1, 2022

Accepted. December 14, 2022

Supplemental Material. DOI: 10.5863/1551-6776-28.6.540.S1

References

1. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*. 2001;286(21):2703–2710.
2. Grover S. Assessment scales for delirium: a review. *World J Psychiatry*. 2012;2(4):58–70.
3. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. *Psychiatry Res*. 1988;23(1):89–97.
4. Smith HAB, Gangopadhyay M, Goben CM, et al. The Preschool Confusion Assessment Method for the ICU: valid and reliable delirium monitoring for critically ill infants and children. *Crit Care Med*. 2016;44(3):592–600.
5. Smith HAB, Boyd J, Fuchs DC, et al. Diagnosing delirium in critically ill children: validity and reliability of the Pediatric Confusion Assessment Method for the Intensive Care Unit. *Crit Care Med*. 2011;39(1):150–157.
6. Traube C, Silver G, Kearney J, et al. Cornell Assessment of Pediatric Delirium: a valid, rapid, observational tool for screening delirium in the PICU. *Crit Care Med*. 2014;42(3):656–663.
7. Patel AK, Bell MJ, Traube C. Delirium in pediatric critical care. *Pediatr Clin N Am*. 2017;64(5):1117–1132.
8. Harris J, Ramelet AS, van Dijk M, et al. Clinical recommendations for pain, sedation, withdrawal and delirium assessment in critically ill infants and children: an ESPNIC position statement for healthcare professionals. *Intensive Care Med*. 2016;42(6):972–986.
9. Smith HAB, Besunder JB, Betters KA, et al. 2022 Society of Critical Care Medicine Clinical practice guidelines on prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility. *Pediatric Crit Care Med*. 2022;23(2):e74–e110.
10. Capino AC, Thomas AN, Baylor S, et al. Antipsychotic use in the prevention and treatment of intensive care unit delirium in pediatric patients. *J Pediatr Pharmacol Ther*. 2020;25(2):81–95.
11. Aljabari S, Carter C, Waheed S, Anderson JE. Practice variability in screening and treating pediatric critical illness delirium: survey. *J Pediatr Intensive Care*. 2020;10(4):271–275.
12. Kudchadkar SR, Yaster M, Punjabi NM. Sedation, sleep promotion, and delirium screening practices in the care of mechanically ventilated children: a wake-up call for the pediatric critical care community. *Crit Care Med*. 2014;42(7):1592–1600.

13. Koizumi T, Kurosawa H. Survey of analgesia and sedation in pediatric intensive care units in Japan. *Pediatr Int*. 2020;62(5):535–541.
14. Guerra GG, Joffe AR, Cave D, et al. Survey of sedation and analgesia practice among Canadian pediatric critical care physicians. *Pediatr Crit Care Med*. 2016;17(9):823–830.
15. Junior JC, de Araujo OR, de Andrade AB, de Cavalho WB. Practices related to assessment of sedation, analgesia, and delirium among critical care pediatricians in Brazil. *Einstein (Sao Paulo).* 2020;18:eAO5168.
16. Mody K, Kaur Savneet, Mauer EA, et al. Benzodiazepines and development of delirium in critically ill children: estimating the causal effect. *Crit Care Med*. 2018;46(9):1486–1491.
17. Madden K, Hussain K, Tasker RC. Anticholinergic medication burden in pediatric prolonged critical illness: a potentially modifiable risk factor for delirium. *Pediatr Crit Care Med*. 2018;19(10):917–924.
18. Traube C, Silver G, Gerber L, et al. Delirium and mortality in critically ill children: epidemiology and outcomes of pediatric delirium. *Crit Care Med*. 2017(5);45:891–898.
19. Traube C, Silver G, Reeder RW, et al. Delirium in critically ill children: an international point prevalence study. *Crit Care Med*. 2017;45(4):584–590.
20. Ng KT, Teoh WY, Khlor AJ. The effect of melatonin on delirium in hospitalized patients: a systematic review and meta-analyses with trial sequential analysis. *J Clin Anesth*. 2019;59:74–81.
21. Laudone TW, Beck SD, Lahr HJ. Evaluation of melatonin practices for delirium in pediatric critically ill patients. *J Pediatr Pharmacol Ther*. 2021;26(4):361–365.
22. Bradford CV, Miller JL, Harkin M, et al. Melatonin use in infants admitted to intensive care units. *J Pediatr Pharmacol Ther.* 2023;28(7): In press.
23. Harrison AM, Lugo RA, Lee WE, et al. The use of haloperidol in agitated critically ill children. *Clin Pediatr*. 2002;41(1);51–54.
24. Ratcliff SL, Meyer WJ, Cuervo LJ, et al. The use of haloperidol and associated complications in the agitated, acutely ill pediatric burn patient. *J Burn Care Rehabil*. 2004;25(6):472–478.
25. Hutchins LM, Shipman A, Zimmerman KO, et al. Evaluation of QTc interval effects of antipsychotic medications for intensive care unit delirium in pediatric patients. *J Pediatr Pharmacol Ther*. 2021;26(1):87–91.
26. Schieveld J, Leroy P, van Os J, et al. Pediatric delirium in critical illness: phenomenology, clinical correlates and treatment response in 40 cases in the pediatric intensive care unit. *Intensive Care Med*. 2007;33(6):1033–1040.
27. Slooff VD, Spaans E, Van puijenbroek E, et al. Adverse events of haloperidol for the treatment of delirium in critically ill children. *Intensive Care Med*. 2014;40(10):1602–1603.
28. Slooff VD, Van den dungen DK, Van beusekom BS, et al. Monitoring haloperidol plasma concentration and associated adverse events in critically ill children with delirium: first results of a clinical protocol aimed to monitor efficacy and safety. *Pediatr Crit Care Med*. 2018;19(2):e112–e119.
29. Kishk O, Simone S, Lardieri AB, et al. Antipsychotic treatment of delirium in critically ill children: a retrospective matched cohort study. *J Pediatr Pharmacol Ther*. 2019;24(3):204–213.
30. Sassano-Higgins S, Freudenberg N, Jacobson J, et al. Olanzapine reduces delirium symptoms in the critically ill pediatric patient. *J Pediatr Intensive Care*. 2013;2(2): 49–54.
31. Turkel S, Jacobson J, Tavare C. The diagnosis and management of delirium in infancy. *J Child Adolesc Psychopharmacol*. 2013;23(5):352–356.
32. Turkel S, Jacobson J, Munzig E, et al. Atypical antipsychotic medications to control symptoms of delirium in children and adolescents. *J Child Adolesc Psychopharmacol*. 2012;22(2):126–130.
33. Traube C, Witcher R, Mendez-Rico E, et al. Quetiapine as treatment for delirium in critically ill children: a case series. *Pediatr Intensive Care*. 2013;2(3):121–126.
34. Traube C, Augenstein J, Greenwald B, et al. Neuroblastoma and pediatric delirium: a case series. *Pediatr Blood Cancer*. 2014;61(6):1121–1123.
35. Joyce C, Witcher R, Herrup E, et al. Evaluation of the safety of quetiapine in treating delirium in critically ill children: a retrospective review. *J Child Adolesc Psychopharmacol*. 2015;25(9):666–670.
36. Groves A, Traube C, Silver G. Detection and management of delirium in the neonatal unit: a case series. *Pediatrics*. 2016;137(3):e20153369.
37. Hughes KM, Thorndyke A, Tillman EM. Incidence of corrected QT prolongation with concomitant methadone and atypical antipsychotics in critically ill children. *J Pediatr Pharmacol Ther*. 2021;26(3):271–276.
38. Campbell CT, Grey E, Munoz-Pareja J, Manasco KB. An evaluation of risperidone dosing for pediatric delirium in children less than or equal to 2 years of age. *Ann Pharmacother*. 2020;54(5):464–469.
39. Cronin MT, Gennaro JL, Watson RS, et al. Haloperidol and quetiapine for the treatment of ICU-associated delirium in a tertiary pediatric ICU: a propensity score-matched cohort study. *Pediatr Drugs*. 2021;23(2):159–169.
40. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27(2):596–601.