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Antipsychotic Drug Prescription in Pediatric Intensive Care Units: A 10-Year U.S. Retrospective Database Study

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Abstract

Delirium recognition during pediatric critical illness may result in the prescription of antipsychotic medication. These medications have unclear efficacy and safety. We sought to describe antipsychotic medication use in pediatric intensive care units (PICUs) contributing to a U.S. national database. This study is an analysis of the Pediatric Health Information System Database between 2008 and 2018, including children admitted to a PICU aged 0 to 18 years, without prior psychiatric diagnoses. Antipsychotics were given in 16,465 (2.3%) of 706,635 PICU admissions at 30 hospitals. Risperidone (39.6%), quetiapine (22.1%), and haloperidol (20.8%) were the most commonly used medications. Median duration of prescription was 4 days (interquartile range: 2–11 days) for atypical antipsychotics, and haloperidol was used a median of 1 day (1–3 days). Trend analysis showed quetiapine use increased over the study period, whereas use of haloperidol and chlorpromazine (typical antipsychotics) decreased ($p < 0.001$). Compared with no antipsychotic administration, use of antipsychotics was associated with comorbidities (81 vs. 65%), mechanical ventilation (57 vs. 36%), longer PICU stay (6 vs. 3 days), and higher mortality (5.7 vs. 2.8%) in univariate analyses. In the multivariable model including demographic and clinical factors, antipsychotic prescription was associated with mortality (odds ratio [OR] = 1.09, 95% confidence interval [CI]: 1.02–1.18). Use of atypical antipsychotics increased over the 10-year period, possibly reflecting increased comfort with their use in pediatric patients. Antipsychotics were more common in patients with comorbidities, mechanical ventilation, and longer PICU stay, and associated with higher mortality in an adjusted model which warrants further study.

Keywords
- antipsychotic
- delirium
- pediatric critical care

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Introduction

Awareness of the prevalence of delirium among children admitted to pediatric intensive care units (PICUs) and pediatric cardiac intensive care units (PCICUs) has been increasing over the past decade.[1–7] This awareness and the availability of pediatric delirium screening tools have led to the development of delirium management pathways which include both nonpharmacologic and pharmacologic approaches.[8–10] When nonpharmacologic measures are insufficient, antipsychotic agents are often suggested. As no antipsychotic agent is approved by the U.S. Food and Drug Administration (FDA) for treatment of delirium in children, antipsychotics are administered off-label in PICUs and PCICUs. Several studies have reported single-center experience with antipsychotics for PICU delirium with varying report of adverse events.[11–14] One study reported adverse events in 9.6% of patients treated with haloperidol, while another study reported a 5% incidence in children prescribed quetiapine, largely QT prolongation.[15,16] No studies have demonstrated efficacy of antipsychotic agents in pediatric delirium; a recent single-center cohort of 27 PICU patients demonstrated worsened delirium scores with haloperidol.[17] Results of several large adult ICU studies have conflicting results regarding benefits to ICU outcomes.[18–20]

Increasing awareness of PICU delirium and more systematic pediatric delirium screening is starting to expand to include other hospitalized pediatric patients. In the context of the lack of published efficacy for delirium, we sought to evaluate recent use of antipsychotics in PICUs and PCICUs, and how it may have changed over the past decade.

Materials and Methods

Study Design and Setting

This retrospective database study used the Pediatric Health Information System (PHIS) database which contains administrative and billing data from 49 tertiary care children's hospitals located in 27 states and the District of Columbia. The PHIS database is maintained by the Children's Hospital Association in Lenexa of Kansas which along with participating hospitals jointly ensures data integrity and quality. The PHIS hospitals provide discharge data, including patient demographics, diagnoses, and procedure codes for all inpatient, observation, emergency department, and ambulatory surgery encounters. Up to 41 International Classification of Diseases, 9th and 10th Revisions (ICD-9 and ICD-10) diagnoses and up to 41 ICD-9 and ICD-10 procedure codes are included. Billing data include medications, radiologic imaging studies, laboratory tests, and supplies charged to each patient. All data are deidentified at the time of data submission, and data are subjected to several reliability and validity checks before being included in the database.

The Children's Healthcare of Atlanta institutional review board and the Children's Hospital Association Board determined this study to be exempt from review because all patient-related data were deidentified before review and analysis.

Study Population

All inpatient and observational encounters of children 18 years of age or less, from January 1, 2008, to December 31, 2018, were collected from 31 hospitals that continuously contributed data to PHIS during the study period. One hospital was excluded for having chlorpromazine administered during a large proportion (~10%) of PICU admissions, compared with less than 2% for all other hospitals, suggesting a potential for data errors. Children admitted to PICUs (and PCICUs, where applicable) with one of the selected antipsychotics were included in the final analysis. Antipsychotics identified for analysis included quetiapine, risperidone, ziprasidone, aripiprazole, olanzapine, chlorpromazine, and haloperidol.

Using all encounters in PHIS before the PICU or PCICU encounter, we excluded children with a concurrent ICD-9 or ICD-10 diagnosis code for a psychiatric condition, including schizotypal disorder, schizophrenia, schizoaffective disorder, delusional disorders, brief psychotic disorders, shared psychotic disorders, unspecified psychosis, mania, bipolar disorders, and major depressive disorders (►**Supplementary Table S1**; available in the online version).

Information about the PICU and hospital course collected included duration of mechanical ventilation, PICU length of stay, hospital length of stay, and hospital mortality. Demographics include age, sex, race and/or ethnicity (non-Hispanic white, non-Hispanic African American, Hispanic, or other), primary insurance payer (government, commercial or self-pay, or unknown), and admission diagnosis. Complex chronic conditions were defined by ICD-9 and ICD-10 codes and derived from hospitalization patterns of children with costly illnesses and congenital defects.[21] Chronic conditions on ICU admission were subcategorized as 0, 1, 2, or more than 3 conditions. The chronic conditions included any of the following: cardiovascular, gastrointestinal, hematologic/immunologic, malignancy, metabolic, neurologic/neuromuscular, congenital, renal/urologic, and respiratory.

Statistical Analysis

Antipsychotic medications were grouped into two categories: typical (haloperidol and chlorpromazine) and atypical (quetiapine, risperidone, ziprasidone, olanzapine, and aripiprazole). Descriptive statistics were calculated for all variables of interest. Categorical variables were summarized as counts or percentages. Continuous variables were summarized as medians with interquartile ranges (IQRs). To explore how patient demographics or antipsychotic use changed over time, we treated the discharge year as an ordinal variable. Differences between admissions with and without antipsychotic use were conducted using cluster-adjusted linear and logistic regression models. The type-3 fixed effect p-value for antipsychotic use as the main predictor was reported from these models. Standardized differences (effect sizes) were used to assess differences between admissions with and without antipsychotic use: effect sizes <0.1 were considered negligible, 0.1 to <0.3 was small, 0.3 to 0.75 was medium and >0.75 was large.

Usage trends were calculated using the Cochran–Armitage trend test with a one-sided p-value for testing increasing

or decreasing trends over discharge years. Cluster-adjusted generalized regression models were used to test for trends over time, while adjusting for correlations of admissions within hospitals. Hospital-level variability of admissions using typical and atypical antipsychotics was tested by including a random intercept for hospital in generalized regression models. Standardized differences (effect sizes) were computed to assess differences between typical versus atypical antipsychotic admissions. A multivariable logistic regression model, also adjusting for admissions nested within hospitals, was used to estimate the adjusted odds of mortality. The main predictor was antipsychotic administration, and covariates that were controlled for included age of patient, sex, race, insurance type, chronic conditions on PICU admission, mechanical ventilation use, and admission type.[22] Analysis was conducted using statistical software (SAS version 9.4, SAS Institute Inc., Cary, North Carolina, United States). Statistical significance was assessed at the 0.05 level.

Results

Population Characteristics

During the study period, 759,659 PICU and PCICU admissions from 31 hospitals were evaluated. After exclusion of patients older than 18 years and those with a psychiatric diagnosis, we identified 16,465 admissions (2.2%) for the antipsychotic subgroup analysis (►**Fig. 1**). Of the 16,465 admissions with antipsychotic use, 11,785 received an atypical antipsychotic, 3,321 received a typical antipsychotic, and 1,359 received

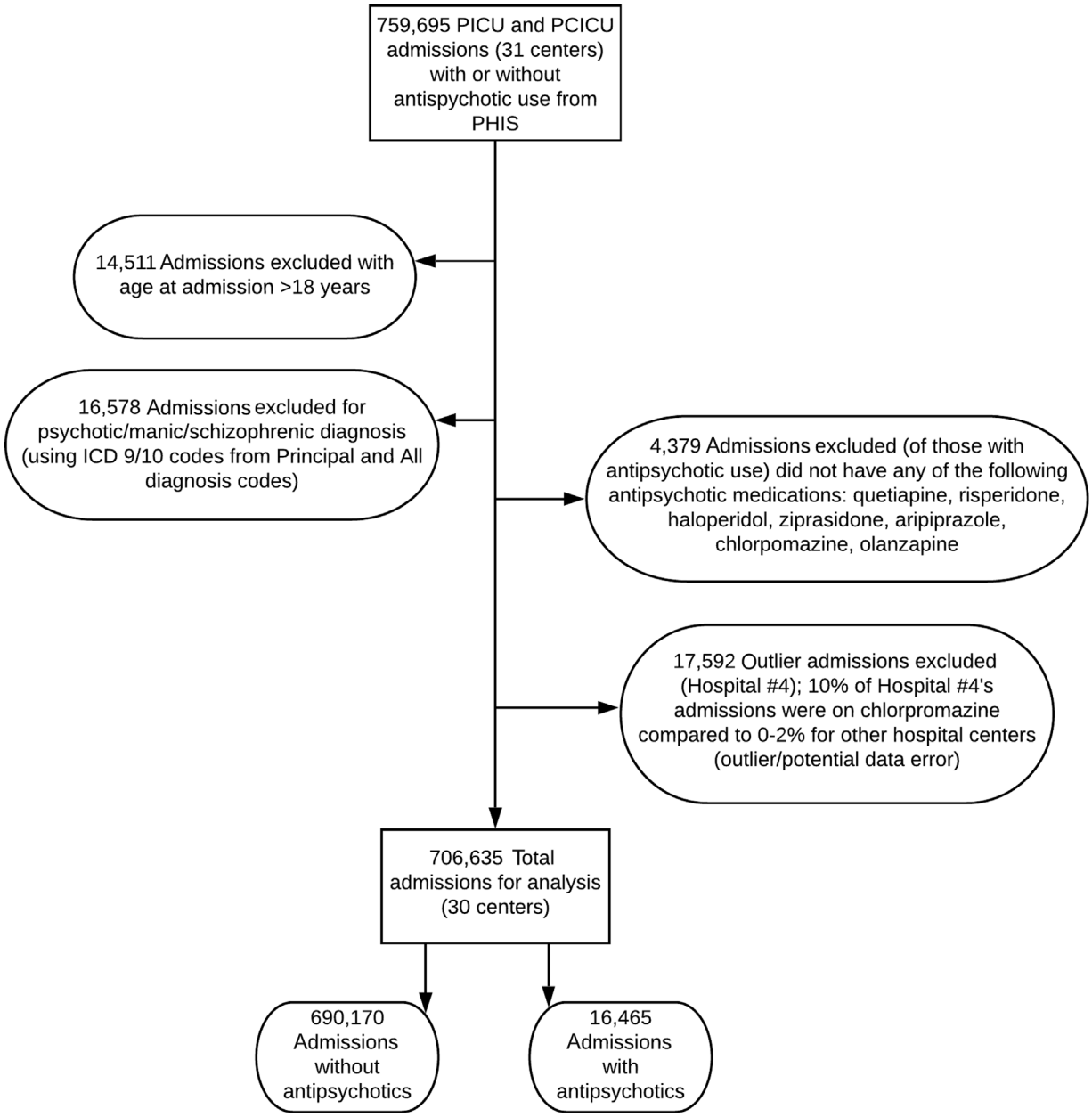

Fig. 1 Cohort flowchart. Details of cohort composition, starting with 759,695 admissions to pediatric intensive care units (PICUs) and pediatric cardiac intensive care units (PCICUs) in 31 centers. Abbreviation: ICD 9/10, International Classification of Diseases, 9th and 10th Revisions.

both. The median age of patients who received antipsychotics was 11 years (IQR: 4–15 years), with 25.5% aged 0 to 4 years, 37.9% female, and 59.0% having government insurance (►**Table 1**). The most common admission diagnoses were respiratory (13.7%), trauma (12.2%), neurologic (10.1%), or other categories (37.8%). Only 19.6% of admissions involved no chronic conditions, and 31.6% had more than two chronic conditions. The median ICU length of stay was 6 (IQR: 2–18) days, and overall hospital mortality was 5.7% (►**Table 1**). The median duration of antipsychotic administration was 4 days (IQR: 2–11 days), and patients received an antipsychotic for 44.4% (IQR: 9.1–100%) of their total ICU days.

Comparison to General Pediatric Intensive Care Unit Population

Use of antipsychotics during PICU admission, compared with no antipsychotics, was associated with older age (11 vs. 3 years; effect size = 0.745), at least one comorbid condition (81vs. 65%; effect size = 0.39), longer PICU (6 vs. 3 days; effect size = 0.35), and hospital length of stay (14 vs. 6 days; effect

Table 1 Clinical characteristics of pediatric intensive care unit (PICU) admissions in which antipsychotic used compared with no antipsychotic medication[a]

Characteristic	All Admissions (N=706,635)	Admissions With Antipsychotics (n=16,465)	No Antipsychotics (n=690,170)	*p*-Value	Effect Size[b]
Age at admission, months median (IQR)	42.6 (8.5-129.8)	136.3 (57.8-184.2)	41.1 (8.2-126.9)	<0.001	0.750
Age groups, years (%)					
0-4	400,092 (56.6)	4,206 (25.5)	395,886 (57.4)	<0.001	0.682
5-9	113,172 (16.0)	2,990 (18.2)	110,182 (16.0)	<0.001	0.058
10-14	111,848 (15.8)	4,671 (28.4)	107,177 (15.5)	<0.001	0.314
15-18	81,523 (11.5)	4,598 (27.9)	76,925 (11.1)	<0.001	0.433
Female sex (%)	313,262 (44.3)	6,248 (37.9)	307,014 (44.5)	<0.001	0.133
Race/ethnicity[c] n(%)					
Non-Hispanic white	356,503 (51.8)	9,618 (59.6)	346,885 (51.6)	<0.001	0.161
Non-Hispanic Black	138,427 (20.1)	2,626 (16.3)	135,801 (20.2)	<0.001	0.102
Hispanic	113,068 (16.4)	2,239 (13.9)	110,829 (16.5)	<0.001	0.073
Other	80,601 (11.7)	1,664 (10.3)	78,937 (11.7)	<0.001	0.046
Insurance n(%)					
Government	404,883 (57.3)	9,710 (59.0)	395,173 (57.3)	<0.001	0.035
Private	265,605 (37.6)	5,999 (36.4)	259,606 (37.6)	<0.001	0.024
Other	36,147 (5.1)	756 (4.6)	35,391 (5.1)	<0.001	0.025
Admission diagnosis n(%)					
Infectious/parasitic	11,696 (1.7)	486 (3.0)	11,210 (1.6)	<0.001	0.089
Hemato-oncologic	30,405 (4.3)	1,005 (6.1)	29,400 (4.3)	<0.001	0.083
Neurologic	54,774 (7.8)	1,669 (10.1)	53,105 (7.7)	<0.001	0.086
Cardiovascular	25,315 (3.6)	756 (4.6)	24,559 (3.6)	<0.001	0.052
Respiratory	119,276 (16.9)	2,257 (13.7)	117,019 (17.0)	<0.001	0.090
Traumatic injury/external causes of injury and exposures	61,411 (8.7)	2,014 (12.2)	59,397 (8.6)	<0.001	0.119
Congenital malformations	112,828 (16.0)	1,594 (9.7)	111,234 (16.1)	<0.001	0.193
Ill-defined symptoms/signs	147,937 (20.9)	3,605 (21.9)	144,332 (20.9)	<0.001	0.024
Other/unknown	142,993 (20.2)	3,079 (18.7)	139,914 (20.2)	<0.001	0.007
Chronic conditions on admission[d] n(%)					
0	243,940 (34.5)	3,221 (19.6)	240,719 (34.9)	<0.001	0.349
1	226,136 (32.0)	4.459 (27.1)	221,677 (32.1)	<0.001	0.111
2	122,957 (17.4)	3,588 (21.8)	119,369 (17.3)	<0.001	0.114
>2	113,602 (16.1)	5,197 (31.6)	108,405 (15.7)	<0.001	0.380

(*Continued*)

Table 1 (*Continued*)

Characteristic	All Admissions (N=706,635)	Admissions With Antipsychotics (n=16,465)	No Antipsychotics (n=690,170)	*p*-Value	Effect Size[b]
PICU LOS, days,[e] median (IQR)	3 (2-6)	6 (2-18)	3 (2-6)	<0.001	0.354
Hospital LOS, days, median (IQR)	6 (4-12)	14.0 (6-37.0)	6 (4-11)	<0.001	0.481
Mechanical ventilation during PICU admission[f] n(%)	257,102 (36.4)	9,341 (56.7)	247,761 (35.9)	<0.001	0.427
Mechanical ventilation, days, median (IQR)	3 (1-8)	8 (2-19)	3 (1-7.35)	<0.001	0.306
Hospital Mortality[g] n(%)	20,348 (2.9)	945 (5.7)	19,403 (2.8)	<0.001	0.145

[a]Data are presented as number (percent) unless indicated by median (25th-75th percentiles). Some percentages do not total to 100 because of rounding.
[b]Effect size: standardized mean difference between the 2 groups. To compare each level, group variables with >2 levels were dummy coded at each level. Cohen D suggested that effect size indexes of 0.20, 0.50, and 0.80 represent small, medium, and large effect sizes.
[c]Missing race: n=18,036 missing for all-admissions group.
[d]Chronic conditions include any of the following: cardiovascular, gastrointestinal, hematologic/immunologic, malignancy, metabolic, neurologic/neuromuscular, congenital, renal/urologic, and respiratory conditions.
[e]Missing ICU length of stay (LOS): n=8,714 missing for all-admissions group.
[f]Denominator is out of those with mechanical ventilation: (n=69,995 missing days on mechanical ventilation if ventilated).
[g]Missing discharge status: n=13,647 missing for all-admissions group.

size = 0.48). Use of antipsychotics during the PICU stay was also associated with mechanical ventilation support (57 vs. 36%; effect size = 0.43), with a median mechanical ventilation duration of 8 days (vs. 3 days in the no-antipsychotic group; effect size = 0.30). In addition, the mortality of PICU admissions with antipsychotic administration was 5.7% compared with 2.8% overall for PICU admissions without antipsychotics (effect size = 0.145). In a multivariable logistic regression model, adjusted for age, sex, race, insurance, chronic conditions, need for mechanical ventilation, and admission diagnosis group, odds ratio (OR) for mortality in PICU patients who received antipsychotics was 1.09 (95% confidence interval [CI]: 1.0–1.18) compared with those who did not (►**Table 2**).

Trends in Antipsychotic Use

As shown in ►**Fig. 2**, over the study period, use of quetiapine and olanzapine significantly increased ($p < 0.001$), whereas use of haloperidol, ziprasidone, and aripiprazole all decreased ($p < 0.001$). Use of risperidone ($p = 0.363$) and chlorpromazine ($p = 0.106$) did not change significantly over the study period when cluster-adjusted by hospital. When grouped as typical versus atypical antipsychotic medications, atypical antipsychotic use increased over the timeframe, and typical antipsychotic administration decreased ($p < 0.001$). When cluster-adjusted by hospitals, both a positive trend in atypical antipsychotics and a negative trend in typical antipsychotics remained ($p < 0.001$).

Variability in Antipsychotic Use across Hospitals

►**Fig. 3** shows the variability in antipsychotic use across the PICUs of the 30 PHIS hospitals included in the study. The PHIS institutions show a wide variability in use of atypical or typical antipsychotics as a percentage of total PICU admissions. For the 30 hospitals, the median proportion of ICU admissions during which a typical antipsychotic was prescribed was 0.45% (IQR: 0.39–0.74%). Atypical antipsychotics were administered in a median of 1.68% of admissions (IQR: 1.38–2.11%) across the 30 hospitals. Use of atypical agents occurred in less than 1% of admissions at two sites (8 and 13) and more than 3% of admissions at sites 16 and 21 (►**Fig. 3**). Although most sites used typical agents in less than 1% of ICU admissions, a couple of sites (8 and 18) used them in more than 2% of admissions (►**Fig. 3**).

Discussion

Increased awareness of ICU delirium has consequently led to questions about delirium management, and the risks and benefits of pharmacologic therapy.[8–17] Results of a recent randomized, double-blind, placebo-controlled trial of haloperidol and ziprasidone in adult ICU patients showed no difference in the duration of delirium.[18] A clinical pathway published by Silver et al[8] suggested a multidisciplinary approach to the prevention and management of delirium in children, and that antipsychotic drugs be given consideration, especially when the child is agitated. Here, we report continued use of antipsychotics in pediatric critical care, and an increasing trend in the atypical agents, like quetiapine and olanzapine, with a decrease in the use of typical agents like haloperidol.

The increase in prescription of atypical antipsychotics in PICU patients is in the context of a lack of FDA approval for use in children under 5 years or for management of delirium in children or adults. Several reports have demonstrated the safe administration of these agents in young children; however, their efficacy in altering clinical outcomes remains in question.[12–17,23] The safety profile of atypical antipsychotics is improved compared with typical agents, with fewer extrapyramidal symptoms, lower incidence of neuroleptic

Table 2 Logistic regression models for odds of mortality with antipsychotic use versus no antipsychotic use

Covariate		OR (95% CI)	*p*-Value
Antipsychotic use	Yes vs. no	1.09 (1.02–1.18)	0.017
Age (y)	0–4	1.01 (0.96–1.06)	<0.001
	5–9	0.78 (0.73–0.83)	<0.001
	10–14	0.89 (0.83–0.94)	<0.001
	15–18	Reference	
Gender	Female vs. male	1.05 (1.02–1.08)	<0.001
Race/ethnicity	White	Reference	
	Black	1.09 (1.05–1.14)	<0.001
	Hispanic	1.1 (1.05–1.15)	<0.001
	Other	1.39 (1.32–1.46)	<0.001
Payer	Private	Reference	
	Government	1.06 (1.03–1.10)	<0.001
	Other	1.71 (1.6–1.8)	<0.001
No. of chronic conditions	0	Reference	
	1	2.53 (2.38–2.69)	<0.001
	2	4.43 (4.17–4.7)	<.001
	>2	5.21 (4.92–5.52)	<0.001
Mechanical ventilation	Yes vs. no	19.6 (18.6–20.7)	<0.001
Admission category	Unknown	Reference	
	Infection	2.09 (1.85–2.37)	<0.001
	Heme-Onc	2.1 (1.92–2.4)	<0.001
	Cardiovascular	0.87 (0.78–0.98)	<0.001
	Neurologic	3.58 (3.33–3.98)	<0.001
	Respiratory	0.76 (0.69–0.85)	<0.001
	Trauma/exposures	2.39 (2.16–2.66)	<0.001
	Congenital	0.57 (0.52–0.64)	<0.001
	Ill-defined symptoms	0.93 (0.84–1.03)	<0.001
	Other	1.21 (1.09–1.34)	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio.

malignant syndrome, less hepatic dysfunction, and fewer drug interactions.[15,24,25] However, adverse effects, such as weight gain, insulin resistance, and hyperlipidemia, do occur.[24,26–29] These develop over a longer period than an usual ICU stay; however, agents started in the ICU may continue after transfer or discharge. Additionally, the impact of these agents on longer term brain development when used in younger children is not completely understood

It was not surprising that one-fourth of antipsychotics were prescribed for children under 4 years of age, because this group is at the highest risk of delirium according to several PICU series.[2,6,30] Likewise, patients receiving mechanical ventilation and with admission diagnoses of trauma or respiratory or neurologic illness were more commonly prescribed antipsychotics in our study. This is similar to the results of an international point prevalence study on delirium in which children receiving antiepileptic medications and those receiving sedation and analgesia were at highest risk of delirium.[2] We also found that a high proportion of admissions with use of antipsychotic agents involved in multiple chronic conditions compared with the general PICU population. This is of interest because Dechnik and Traube[31] reported that patients with preexisting chronic conditions, poor nutritional status, or cognitive or neurologic disabilities are at higher risk of delirium.

While antipsychotic prescription was associated with increased comorbidity, ventilation, and longer PICU length of stay, controlling for these features in the multivariable model demonstrated a persistent relationship between antipsychotic administration and mortality. Data limitation does not allow us to imply a cause and effect relationship to the antipsychotic agent. It is likely a combined effect of increased comorbidities, complexity of PICU admission, and mechanical ventilation, all associated with increased delirium leading to antipsychotic use. The high rate of chronic comorbidities in the PICU population reported here also

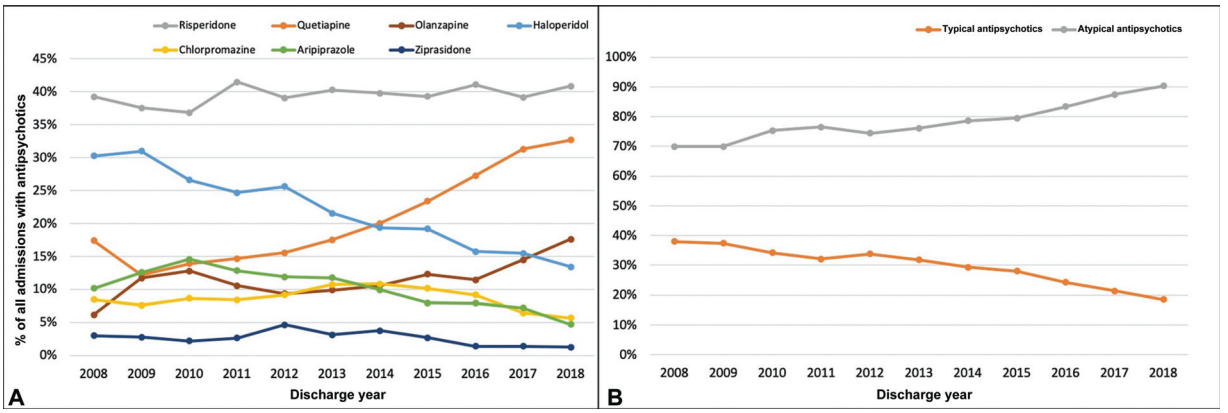

Fig. 2 Trends of antipsychotic use, 2008–2018. Pediatric intensive care unit (PICU) and pediatric cardiac intensive care unit (PCICU) admissions for 16,465 children using Cochran-Armitage trend test. (**A**) Specific antipsychotics. Positive trends for quetiapine, risperidone, and olanzapine. (**B**) Typical versus atypical antipsychotics. Positive trend for atypical antipsychotics ($p < 0.001$).

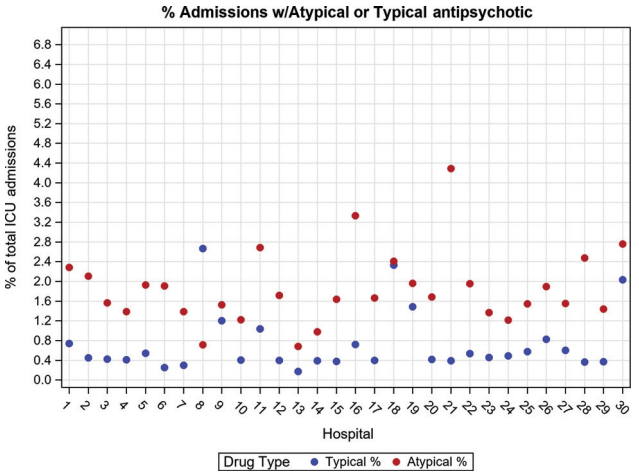

Fig. 3 Proportion of pediatric intensive care unit (PICU) admissions with antipsychotic use by hospital. Each of the 30 pediatric health information system database centers is designated by a hospital number.

likely reflects a degree of polypharmacy in these patients, and a high risk of drug interaction. We believe this relationship deserves future study. Although there are limitations of using mortality as the outcome measure for pediatric critical illness, limitations of the data available in the PHIS database meant we were unable to fully explore other potential outcomes in the cohort.

Interestingly, patients who received antipsychotic agents did so for almost 45% of their PICU length of stay. The duration of use for quetiapine in this study was 6 days (IQR: 3–15 days), much lower than reported in a prior study in which median quetiapine use was 12 days (IQR: 4.5–22 days) in critically ill children.[12] We also report a variability in the use of antipsychotics (typical vs. atypical) across the PHIS hospitals, with use of atypical agents ranging from less than 1% to more than 3% of ICU admissions, and typical agents in less than 1% to more than 2% of admissions. This variability likely reflects varying case mix across hospitals, as well as comfort in the diagnosis of delirium, pharmacologic treatment of delirium, atypical versus typical agents, and use of nonpharmacologic therapies.

Limitations

There are several limitations to using the PHIS database which have previously been described by other studies.[32,33] It is an administrative database, and although it provides more therapeutic and diagnostic data per patient than most administrative datasets, no physiologic data are available. Because the children's hospitals participating in the PHIS are tertiary and quaternary care facilities in major metropolitan cities in the United States, the data are likely not generalizable to community hospitals or hospitals that do not offer specialty pediatric services. We were also not able to look at the continuation of antipsychotics after ICU discharge or transfer or to compare the trends in antipsychotic use in pediatric critical care to wider inpatient and outpatient usage of these medications. Furthermore, the study is subject to the limitations of all observational analyses including selection bias, residual confounding, and measurement error. There may be inherent differences in the coding practices among PHIS-participating hospitals that contribute to selection bias which may be minimized by the use of previously described and, in some cases, validated ICD-9 and ICD-10 codes. Because these codes notoriously insufficient to measure true incidence of diagnoses in hospitalized patients, we were not able to accurately measure rates of delirium diagnosis and the relationship of that timing to antipsychotic administration, so we chose not to interrogate the assignment of delirium diagnosis codes in this cohort. We are not able to definitively report that these antipsychotics were all administered to treat delirium, although that is our experience of their use as PICU clinicians.

Conclusion

Over the past 10 years, use of atypical antipsychotics, including quetiapine and olanzapine, have increased, whereas haloperidol use has decreased. This may reflect increasing comfort with atypical agents which are not FDA approved in the treatment of delirium. Chronic comorbidities and mechanical ventilation support were associated with greater odds of antipsychotic medication use in the PICU, and

antipsychotic use was correlated with higher mortality when controlling for other available clinical factors. Because of limitations to the database, we are not able to draw a cause and effect relationship between antipsychotic use or delirium and mortality; however, further study is needed to systematically assess this relationship in critically ill patients.

Authors' Contributions

K.M., R.C.T., J.F., C.M., and P.K. participated in the concept and design, analysis and interpretation of data, and drafting or revising of the manuscript. M.W. and M.H. participated in interpretation of data and revising of the manuscript. All authors have approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interest

None delcared.

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