Original Article

Trends in Pharmaceutical Sciences and Technologies 2026: 12(1):93-102.

Drug-Drug Interactions Among Pediatric Intensive Care Unit: Risk Factors and Clinical Outcomes

Hosein Abbasi[1†];PharmD, Afsaneh Vazin[1†];PharmD, PhD, Seyed Mohammad Iman Moezzi[2];PharmD, PhD, Negar Ahvar[1]; PharmD, PhD, Eslam Shorafa[3];MD, Katayoon Hojabri[3];MD, Seyedeh Narjes Abootalebi[3];MD, Fatemeh Javanmardi[4];PhD, Mojtaba Shafiekhani[1*];PharmD, Ph.D

[1]Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.
[2]Department of Pharmaceutics, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
[3]Department of Pediatrics, Division of Intensive Care Unit, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.
[4]Department of Biostatistics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.

† These authors contributed equally to this work and share first authorship.

Abstract

Drug–drug interactions (DDIs) are a common concern in pediatric intensive care units (PICUs) and may increase the risk of medication-related adverse events. This study aimed to determine the frequency, categories, and associated factors of potential DDIs in a PICU. We conducted a cross-sectional study between June 2022 and February 2023 among children admitted for at least 48 hours to medical or surgical PICUs who received two or more prescribed medications. Potential DDIs were identified and classified using Lexi-Interact®. Demographic and clinical data, as well as medication-related information, were collected prospectively, and severity and reliability ratings were recorded. Associations with potential DDIs were analyzed using univariable and multivariable logistic regression. Among 345 included patients, 1,858 potential DDIs were detected, including 1,248 (67%) category C interactions, 529 (29%) category D interactions, and 81 (4%) category X interactions. Potential DDIs were more frequent in the medical PICU than in the surgical PICU. The most frequent contraindicated (category X) interaction involved linezolid–methadone. In multivariable analysis, the number of prescribed drugs, use of sedative agents, and PICU type were significantly associated with the occurrence of potential DDIs. In conclusion, potential DDIs were common in this PICU cohort. Polypharmacy, particularly involving sedative agents, was an important modifiable factor associated with potential DDIs. Enhanced monitoring and medication review may help identify and manage high-risk potential DDIs in critically ill pediatric patients.

Keywords: Pediatrics, Critical care, Intensive care unit, Drug Interactions, Medication Errors.

Please cite this article as: Abbasi H, Vazin A, Moezzi SMI, Ahvar N, Shorafa E, Hojabri K, *et al*. Drug-drug interactions among pediatric intensive care unit: Risk factors and clinical outcomes . Trends in Pharmaceutical Sciences and Technologies. 2026;12(1):93-102. doi: 10.30476/tips.2026.110716.1351

1. Introduction

Drug-drug interactions (DDIs) are one of the main reasons for medical errors which can cause a wide range of clinical outcomes, from minor to life-threatening effects (1). DDIs are defined as any alteration in a drug's effect because of another drug. DDIs are mainly classified as pharmacokinetic and pharmacodynamic interactions, although physico-

Corresponding Author: Mojtaba Shafiekhani, Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
Email: mojtabashafiekhani@gmail.com

Received: 21/10/2025; Accepted: 01/03/2026

chemical and pharmaceutical interactions are present, too. DDIs are an important component of medication-related problems and are considered among the preventable causes of medication errors (2).

Drug–drug interactions have also been reported as a contributing factor to preventable adverse drug reactions leading to hospital admission (3). Drug-drug interactions represent an important cause of adverse drug events and may contribute to hospital admissions. Previous studies have reported that drug interactions may account for up to 21% of adverse drug event-related hospital admissions (4). In the pediatric setting, the frequency of DDIs was found to be 59.4-75.2% which is similar to that reported in adult ICU (5-7).

As a result, this study aimed to identify, categorize, and analyze the prevalence and categories of potential DDIs in the pediatric intensive care unit (PICU) of Namazi Hospital, the largest referral center in the south of Iran.

2. Materials and Methods

2.1. Study design

This observational, cross-sectional study was conducted in Namazi Hospital, on hospitalized children in both medical and surgical intensive care units (ICU) from June 2022 to February 2023. The medical PICU has 18 and the surgical PICU has 8 beds. Inclusion criteria of this study were the age of 31 days to 18 years old, hospitalization of more than 48 hours, and having at least two prescribed drugs. Patients with incomplete data were excluded. Ethics approval was obtained from the Ethics Committee of Shiraz University under the ethics code of IR.SUMS.REC.1401.384. In every step, the study's actions were according to the guidelines of the Declaration of Helsinki (1975) (8).

2.2. Data collection

Demographic data including age, sex, cause of admission, and comorbidities, medical history, were collected by the pharmacist. Clinical and laboratory data including length of ICU stay, duration of mechanical ventilation, and mortality were recorded during ICU admission, too.

2.3. DDIs evaluation

For the evaluation of potential DDIs, Lexi-Interact® online software was set as a reference, and based on this, category C, D, and X potential DDIs were chosen (Table 1). All prescribed medications for each patient were entered into the Lexi-Interact software and consequently, detected DDIs were reported. The severity (major, moderate, and minor) and reliability (excellent, good, fair, and poor) of interactions were investigated, too. Since this study focused on software-detected po-

Table 1. DDIs classification and the definition of each class.

DDI classification	Definition
Category A	There is no interaction in the concomitant use of the drugs.
Category B	There might be an interaction in concomitant use of the drugs, but it is not serious, and no intervention is required.
Category C	In the case of concomitant use of the drugs, the patient should be monitored.
Category D	There is a serious interaction in concomitant use of the drugs and further interventions are necessary.
Category X	The concomitant use of the drugs is prohibited.
Minor	Negligible clinical effect or an increase in the frequency and severity of adverse drug reactions might be observed, but there is no need for change in the basis of treatment.
Moderate	Substitution of drugs is necessary, otherwise, the patient's condition might be worsened.
Major	Medical intervention is necessary to reduce adverse drug reactions, otherwise, it could be life-threatening.

tential DDIs, clinically confirmed DDI-related outcomes were not systematically assessed.

2.4. Data analysis

Statistical analysis was performed using SPSS 22.0. Descriptive data were presented as frequency and percentage for categorical variables. Quantitative variables with normal distribution were reported as mean ± standard deviation (SD), whereas non-normally distributed variables were presented as median (interquartile range [IQR]). Comparisons between medical and surgical PICUs were performed using the independent t-test for continuous variables and the Chi-square test for categorical variables. Potential risk factors of DDIs were evaluated using univariable and multivariable logistic regression analyses. Variables with a p-value <0.2 in the univariable analysis were entered into the multivariable logistic regression model. A p-value <0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical data

In this 8-month study, 408 patients were admitted and among them, 63 were excluded due to prescription of one or no drugs or hospitalization for less than 48 hours, so, 345 patients were included. 56.8% of patients were male and their mean age was 65±60 months. 238 (69%) and 107 (31%) patients were hospitalized in the medical and surgical PICU, respectively. Pneumonia (27.8%), convulsion (10.1%), and gastro-enteral problems (GE) (9.7%) were the three top causes of admission among all patients. Cardiovascular problems (3.8%), glucose-6-phosphate dehydrogenase (G6PD) deficiency (3.5%), and cerebral palsy (2.6%) were the most frequent comorbidities. The mean length of hospital and PICU stay were 32.4±26.8 days and 12.57±10.35 days, respectively. Among all 43, 127 investigated medical orders in both wards, 16211 were pharmaceutical orders. Each patient had on average 134±125.3 medical orders, ranging from 10 to 967. Among these, 52.03±46.93 were drug orders, which ranged from 3 to 381. Among all patients, 33% had a CVC, 18.8% had an abdominal catheter, and 73% had a urinary

Catheter. Regarding clinical outcome, 295 patients (85.5%) survived and 50 (14.5%) patients died. The demographic and clinical data of the study population are summarized in Table 2.

The five most prescribed drugs in medical PICU were Pantoprazole (n=210, 88%), Vancomycin (n=170,71%), Meropenem (n=165, 69%), Potassium chloride (n=150, 63%), and Sodium chloride (n=122, 51%). In surgical PICU, Potassium chloride (n=93, 87%), Pantoprazole (n=90, 84%), Acetaminophen (n=74, 69%), Vancomycin (n=61, 57%), and Meropenem (n=58, 54%) were the most commonly prescribed drugs.

3.2. Drug-drug interactions

Among all 345 patients, 278 patients (80%) experienced at least one potential DDI. In total, 1,858 DDIs were detected, 1248 (67.1%) were in the C category, 529 (28.5%) were in the D category, and 81 (4.3%) were in the X category. 1,490 (80.1%) DDIs were in medical PICU and 368 (19.8%) were in the surgical PICU. With respect to the category C potential DDIs, 81% were in the medical ICU, while the remaining 19% were in the surgical ICU. Regarding categories D and X, the percentage of DDIs in the medical ward was 79.2% and 70.2%, respectively. The number of DDIs was significantly (p-value<0.001) higher in the medical ICU (N=205) in comparison to the surgical PICU (N=73) (Table 3).

A combination of multivitamins and Pantoprazole was the most frequent DDI in category C (N=40,3.3%). Midazolam +Fentanyl (N=61, 11.53%) and Linezolid +Methadone (N=12, 14.8%) were the most frequent DDIs in categories D and X, respectively.

In the case of severity of the detected DDIs, among all the DDIs, 452 (24.32%) were

Table 2. Demographic and clinical data of pediatrics admitted to medical or surgical pICUs.

Variable	Ward	Categories	N (%) -mean±SD	p-value
Sex	Medical	Male	128 (53.8)	0.101
		Female	110 (46.2)	
	Surgical	Male	68 (63.6)	
		Female	39 (36.4)	
Age (Mean±SD)	Medical	N/A	63.46±61.71	0.377
	Surgical		69.71±58.42	
number of orders	Medical	N/A	151.27±146.66	< 0.001
	Surgical		66.58±57.66	
number of prescribed drugs	Medical	N/A	14.34±7.87	0.004
	Surgical		11.87±6.18	
Cause of admission	Medical	Pneumonia	73 (30.7)	0.612
		Others	31 (13.0)	
		Seizure	34 (14.3)	
		DKA	29 (12.2)	
		CHD	15 (6.3)	
		Drug poisoning	14 (5.9)	
		Liver failure	13 (5.5)	
		GE	8 (3.4)	
		Sepsis	8 (3.4)	
		Renal failure	7 (2.9)	
		Trauma	6 (2.5)	
	Surgical	Trauma	27 (25.2)	
		GE	26 (24.3)	
		Pneumonia	23 (21.5)	
		Others	14 (13.1)	
		Liver	8 (7.5)	
		Hydatid cyst	7 (6.5)	
		CHD	1 (0.9)	
		Seizure	1 (0.9)	
Status of life	Medical	Alive	192 (80.7)	0.013
		Expired	42 (17.6)	
	Surgical	Alive	99 (92.5)	
		Expired	8 (7.5)	

DKA: Diabetic ketoacidosis; GE: Gastroenteritis; CHD: Congestive heart failure.
DDI: drug-drug interaction, p-value*; compare between two wards

major, 1215 (65.39%) were moderate, and 191 (10.27%) were minor. The reliability of the detected DDIs was analyzed, too. In category C, 8.3% were excellent, 29.6% of them good, 59.3% fair, and 2.7% poorly reliable DDIs were found. These numbers for category D were 18%, 14%, 67%, and (1%), respectively. The reliability of DDIs in category X was 7.5% good and 92.5% fair DDIs based on Lexi-Interact.

Linezolid + Methadone was the most common category X-type DDI (N=12, 14.8%), which may result in an increased possibility of serotonin syndrome. To prevent this DDI, a 14-day interval between the administration of these drugs or the use of another narcotic has

Table 3. Frequency of drug-drug interaction among pediatrics admitted to surgical or medical words.

Ward	Variable	Total (N) (range)	Mean±SD per patient	p-value*
Medical	DDI	1491	6.26±6.93	<0.001
	Number of DDI-C	1013 (0-25)	4.25±4.56	<0.001
	Number of DDI-D	421 (0-11)	1.77±2.38	<0.001
	Number of DDI-X	57 (0-3)	0.24±0.59	
Surgical	Number of DDI	367	3.44±4.73	0.81
	Number of DDI-C	235 (0-22)	2.20±3.53	
	Number of DDI-D	108 (0-5)	1.01±1.23	
	Number of DDI-X	24 (0-3)	0.22±0.52	

been suggested. Domperidone + Fluconazole and Domperidone + Methadone were the cause of 8.6% of category X-type DDIs (N=7). A combination of Fluconazole and Domperidone can increase the risk of QT prolongation. It is suggested to avoid the concomitant use of these drugs, whenever possible.

Diazepam + Metronidazole caused of X-type DDIs in 6 cases (7.3%), which is because of disulfiram-like reactions in the presence of Metronidazole and the parenteral formulation of Diazepam that contains propylene-glycol. There should be a 3-days interval between the administration of these drugs or the use of other benzodiazepines rather than diazepam. Oral Potassium chloride + Ipratropium bromide (N=5, 6.2%) should be avoided, due to reduced gastric motility in response to anticholinergic drugs and increased ulcerogenic side effects of Potassium chloride.

3.3. Potential risk factors of DDIs

As shown in Table 4, patients who experienced DDIs had a significantly (p-value<0.001) higher number of medical orders (144.75±142.08 vs. 43.9±24.58), higher number of pharmaceutical orders (54.77±55.05 vs. 14.69±8.90), and higher number of prescribed drugs (15.22±7.31 vs. 6.75±2.75) in comparison to those who did not. The number of sedative (1.18±1.01 vs. 0.22±0.42, p-value<0.001) and anticonvulsant (1.01±1.37 vs. 0.06±0.23, p-value<0.001) drugs were significantly different in these groups, too. Length of hospital stay (27.74±31.79 vs. 23.06±35.7 days, p-value<0.001), length of ICU stays (12.08±13.42 vs. 3.19±1.56 days, p-value<0.001), and duration of mechanical ventilation (6.67±11.05 vs. 0.45±1.07 days, p-value<0.001) were among other variables that were significantly different between with and without DDIs patients. In the multivariable analysis, the number of prescribed drugs, use of sedative agents, and type of PICUs (medical versus surgical) showed significant associations with the occurrence of potential DDIs.

4. Discussion

DDIs are actually an inevitable part of pharmacotherapy. They can cause adverse drug reactions, increase the duration of hospitalization, costs for patients and the health system, and even death (7). Nevertheless, most DDIs are preventable (9). To our knowledge, this is the first study about DDIs in the PICU in Iran. Among 16, 211 investigated medical orders, 1,858 DDIs were found and 67.1% were category C, 28.5% were category D, and 4.3% were category X.

About 81% of 345 patients included in the present study experienced at least one DDI. In a cross-sectional study on 411 patients at a PICU in Pakistan in 2017, DDIs were experienced by 59% of patients. Age, number of prescribed drugs, and duration of hospital stay were the most important risk factors for the occurrence of DDIs (6). In another study conducted on 88 pediatric patients in Mexico in

Table 4. Univariate and multivariate logistic regressions for risk factors on the occurrence of drug-drug interactions among pediatrics.

Variables	Patients with DDIs	Patients without DDIs	Univariate regression			Multivariate regression		
	Mean±SD	Mean±SD	Crude odds ratio	95% C.I.	p- value	Adjusted odds ratio	95% C.I.	p- value
Number of prescribed drugs	15.22±7.31	6.75±2.75	1.565	1.387-1.765	<0.001	1.357	1.154-1.597	<0.001
Number of orders	144.75±142.08	43.09±24.58	1.040	1.027-1.054	<0.001	0.991	0.956-1.027	0.607
Number of pharmaceutic al orders	54.77±55.05	14.69±8.90	1.140	1.094-1.187	<0.001	1.033	0.933-1.145	0.529
Number of sedatives	1.18±1.01	0.22±0.42	4.755	2.856-7.919	<0.001	2.307	1.102-4.831	0.027
Number of anticonvulsant	1.01±1.37	0.06±0.23	7.111	2.813-17.976	<0.001	2.361	0.814-6.853	0.114
Number of previously used drugs	0.55±1.44	0.25±0.63	1.294	0.940-1.781	0.114	N/A	N/A	N/A
Length of hospitalization	27.74±31.79	23.06±35.07	1.005	0.995-1.015	0.294	N/A	N/A	N/A
Length of ICU stay	12.08±13.42	3.19±1.56	1.757	1.460-2.114	<0.001	1.227	0.961-1.565	0.101
Length of ventilation	6.67±11.05	0.45±1.07	1.790	1.428-2.243	<0.001	0.914	0.635-1.315	0.629
Ward (medical)	238 (69%)	107 (31%)	2.893	1.672-5.007	<0.001	3.198	1.266-8.083	0.014
Sex (male)	196 (56.8%)	149(43.2%)	0.683	0.393-1.187	0.176	N/A	N/A	N/A
Comorbidity (yes)	70 (18.6%)	275(73.3%)	0.472	0.214-1.041	0.063	N/A	N/A	N/A
CVC (yes)	114 (33%)	231 (67%)	5.363	2.364-12.168	<0.001	1.915	0.634-5.784	0.249
Urinary catheter (yes)	266 (77.1%)	79 (22.9%)	2.934	1.653-5.207	<0.001	0.949	0.400-2.252	0.905

2020, it was found that 42% of patients experienced at least one DDI . Smaller sample sizes, fewer average prescribed drugs (4.6±2.8) in the Mexico study (which reduces the odds of

DDIs), and different references for the evaluation of DDIs might be the reasons for less prevalence that is reported (10).

Based on multivariate regression analysis, we found that the number of prescribed drugs, number of sedatives, and wards of hospitalization were independent risk factors for DDIs. Similar results have been shown in the Choi et. Al retrospective study in PICU (7). A systematic review from Iran similarly highlighted the high prevalence of DDIs in both inpatient and outpatient settings and emphasized the importance of identifying factors associated with their occurrence (11).

These findings are in line with results of the study by Dai *et al.* on 54.549 pediatric patients in PICU of 42 hospitals in the US. They found that sedative drugs were included in 30% of recorded DDIs. Similarly, the most used sedative drugs in this study were midazolam and fentanyl (5).

Another factor associated with the occurrence of potential DDIs in this study was the type of ward. DDIs were more frequently observed in the medical PICU than in the surgical PICU. Moreover, anticonvulsant drugs were used significantly more often in the medical ward (p- value<0.001). Previous studies have also identified anticonvulsant medications as important contributors to potential DDIs in pediatric intensive care settings. In a study on Indian children hospitalized in a PICU, therapeutic failure associated with anticonvulsant drugs interactions was reported as the third most important common potential outcome of DDIs (12).

In this study, we could not find any significant association between the demographics (age and sex) of patients and the occurrence of DDIs. Regarding age, Lima et al.'s study on 143 patients in PICU did not find any significant link between demographics and the risk of DDIs (13). Similar results were found in a study on 384 Ethiopian children in ICU in 2016 (14). On the contrary, some studies found differences between the occurrence of DDIs in males and females (15-17). For instance, in a study on 159 children in an ICU in Seoul, they found that the risk of DDIs was 2.2-fold higher in boys in comparison to girls (7).

The most common category X DDI in this study was the interaction between linezolid and methadone which methadone potentiates the serotonergic effect of linezolid that could result in serotonin syndrome. Several case reports and case series have described serotonin syndrome following the concomitant administration of linezolid and methadone, supporting the clinical relevance of this interaction. These findings emphasize the importance of careful monitoring when these medications are prescribed together (18, 19). In Choi et. al's study, the interaction between sildenafil and nitroglycerin was the most common contraindicated DDI and the combination of midazolam and remifentanil was the most common DDI with major severity (7). The interaction between furosemide and gentamicin was the most common DDI with major severity in Getachew et al. study (14). Dai *et al*. reported the interaction of fluconazole and ondansetron as the most common contraindicated DDI (5). Different common causes of admission, diagnosis, co-morbidities, and the preference of physicians for choosing drugs are the main reasons for the variation in main DDIs between these studies. Moreover, it is important that these studies reported the DDIs only based on severity and reliability and did not categorize them based on common C, D, and X categories.

An important strength of this study is its attempt to investigate DDIs specifically in the critically ill pediatric population. On the other hand, this study has a number of limitations, for example, we only investigated the frequency of DDIs in two ICUs. Moreover, only potential DDIs were addressed due to the type of study and the real clinical relevance of the detected DDIs remains unknown. Therefore, the clinical significance of detected DDIs

and appropriate preventive strategies should be assessed individually.

Another limitation of this study was the lack of information regarding the exact onset time of potential DDIs during hospitalization. In addition, pharmaceutical incompatibilities were not evaluated, and only potential drug–drug interactions identified through Lexi-Interact® were assessed.

Future multicenter studies with larger sample sizes are recommended to evaluate the clinical relevance of potential DDIs and to investigate the impact of DDIs on patient outcomes in pediatric intensive care settings.

5. Conclusion

In this cross-sectional study, 80.6% of patients experienced at least one potential DDI during their hospitalization in either surgical or medical PICU. Among all the DDIs, 67.1% were category C, 28.47% were category D, and 4.3% were category X. The number of prescribed drugs, number of sedative agents, and type of PICUs (medical versus surgical) were independent risk factors of DDIs. The interaction between linezolid and methadone in category X, and midazolam and fentanyl in category D were the most common potential DDIs found in this study.

Authors contributions

All authors contributed to the conception, design, data collection, analysis, and drafting of the manuscript. All authors reviewed and approved the final version of the manuscript.

Human Ethics

The study adhered to the principles of the Helsinki Declaration and ICMR Guidelines.

Ethics Approval

Approved by the Institutional Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1401.384).

Trial Registry

Not applicable.

Data Availability Statement

Data will be made available upon reasonable request from the corresponding author.

Acknowledgement

The authors would like to thank Shiraz University of Medical Sciences for their support.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Mehrpooya M, Taher A, Golgiri A, Mohammadi Y, Ahmadimoghaddam D. Evaluation of the Drug Interactions Frequency and Their Related Factors in Hospitalized Patients of the Intensive Care Unit in the Hamadan Besat Hospital. *Avicenna J Nurs Midwifery Care.* 2021;29(3):171-180. doi: 10.30699/ajnmc.29.3.171
2. Ghasemiyeh P, Borhani-Haghighi A, Karimzadeh I, Mohammadi-Samani S, Vazin A, Safari A, *et al*. Major Neurologic Adverse Drug Reactions, Potential Drug-Drug Interactions and Pharmacokinetic Aspects of Drugs Used in COVID-19 Patients with Stroke: A Narrative Review. *Ther Clin Risk Manag.* 2020 Jun 30;16:595-605. doi: 10.2147/TCRM.S259152. PMID: 32669846; PMCID: PMC7335700.
3. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. *Ann Pharmacother*. 2002;36(9):1331-6. doi: 10.1345/aph.1A333. PMID: 12196047.
4. Roughead EE, Kalisch LM, Barratt JD, Gilbert AL. Prevalence of potentially hazardous drug interactions amongst Australian veterans. *Br J Clin Pharmacol.*

2010;70(2):252–7. doi:10.1111/j.1365-2125.2010.03694.x.
5. Dai D, Feinstein JA, Morrison W, Zuppa AF, Feudtner C. Epidemiology of Polypharmacy and Potential Drug-Drug Interactions Among Pediatric Patients in ICUs of U.S. *Children's Hospitals*. *Pediatr Crit Care Med*. 2016;17(5):e218-28. doi: 10.1097/PCC.0000000000000684. PMID: 26959349; PMCID: PMC5243142.
6. Ismail M, Aziz S, Noor S, Haider I, Shams F, Haq I, *et al*. Potential drug-drug interactions in pediatric patients admitted to intensive care unit of Khyber Teaching Hospital, Peshawar, Pakistan: A cross-sectional study. *J Crit Care*. 2017;40:243-250. doi: 10.1016/j.jcrc.2017.04.028. Epub 2017 Apr 22. PMID: 28458171.
7. Choi YH, Lee IH, Yang M, Cho YS, Jo YH, Bae HJ, *et al*. Clinical significance of potential drug-drug interactions in a pediatric intensive care unit: A single-center retrospective study. *PLoS One.* 2021;16(2):e0246754. doi: 10.1371/journal.pone.0246754. PMID: 33556128; PMCID: PMC7870058.
8. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-4. doi: 10.1001/jama.2013.281053. PMID: 24141714.
9. Malfará M, Pernassi M, Aragon D, Carlotti A. Impact of the clinical pharmacist interventions on prevention of pharmacotherapy related problems in the paediatric intensive care unit. *Int J Clin Pharm.* 2018;40(3):513-519. doi: 10.1007/s11096-018-0632-x. Epub 2018 Mar 30. PMID: 29603074.
10. Medina-Barajas F, Vázquez-Méndez E, Pérez-Guerrero EE, Sánchez-López VA, Hernández-Cañaveral II, Gabriel A RO, *et al*. Pilot study: Evaluation of potential drug-drug interactions in hospitalized pediatric patients. *Pediatr Neonatol.* 2020;61(3):279-289. doi: 10.1016/j.pedneo.2019.11.006. Epub 2019 Nov 22. PMID: 31866496.
11. Nabovati E, Vakili-Arki H, Taherzadeh Z, Hasibian MR, Abu-Hanna A, Eslami S. Drug-drug interactions in inpatient and outpatient settings in Iran: a systematic review of the literature. *Daru*. 2014;22:52. doi:10.1186/2008-2231-22-52.
12. Rao C, Shenoy V, Udaykumar P. Potential drug-drug interactions in the pediatric intensive care unit of a tertiary care hospital. *J Pharmacol Pharmacother.* 2019;10(2):63-8. doi:10.4103/jpp.JPP_27_19.
13. Lima EDC, Camarinha BD, Ferreira Bezerra NC, Panisset AG, Belmino de Souza R, Silva MT, *et al*. Severe Potential Drug-Drug Interactions and the Increased Length of Stay of Children in Intensive Care Unit. *Front Pharmacol.* 2020;11:555407. doi: 10.3389/fphar.2020.555407. PMID: 33343344; PMCID: PMC7744879.
14. Getachew H, Assen M, Dula F, Bhagavathula AS. Potential drug–drug interactions in pediatric wards of Gondar University Hospital, Ethiopia: A cross sectional study. *Asian Pac J Trop Biomed*. 2016;6(6):534-8. doi: 10.1016/j.apjtb.2016.04.002
15. Gagne JJ, Maio V, Rabinowitz C. Prevalence and predictors of potential drug-drug interactions in Regione Emilia-Romagna, Italy. *J Clin Pharm Ther.* 2008;33(2):141-51. doi:10.1111/j.1365-2710.2007.00891.x
16. Moura CS, Acurcio FA, Belo NO. Drug-drug interactions associated with length of stay and cost of hospitalization. *J Pharm Pharm Sci.* 2009;12(3):266-72. doi: 10.18433/j35c7z. PMID: 20067703.
17. Cremades J, Gonzalo M, Arrebola I. Relationship between drug interactions and drug-related negative clinical outcomes. *Pharm Pract (Granada)*. 2009;7(1):34-9. doi: 10.4321/s1886-36552009000100005. Epub 2009 Mar 15. PMID: 25147590; PMCID: PMC4139754.
18. Huang J, Edrees H, Lee G. A Case Series on Serotonin Syndrome from Concomitant use of linezolid With Methadone, Buprenorphine, and/or Dextroamphetamine. *J Pharm Pract.* 2024;37(3):780-785. doi: 10.1177/08971900231182772. Epub 2023 Jun 9. PMID: 37295073.

19. Masbough F, Roshanzamiri S, Rahimi M, Sahraei Z, Evini PET. Serotonin syndrome due to concomitant use of linezolid and methadone. *Clin Case Rep*. 2022;10(11):e6341. doi: 10.1002/ccr3.6341.