



Polypharmacy And Drug Interactions in Pediatric Prescribing

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SUMMARY

Introduction: The study addresses the escalating concern of pediatric polypharmacy and potential drug-drug interactions (pDDIs) in the context of pediatric care, where uncertainties regarding medication combinations and safety checks are prevalent. Despite the rising incidence of chronic diseases among children, limited research exists on pediatric polypharmacy, with varying prevalence rates reported globally.

Aim: The Aim of the study is to estimate the prevalence of polypharmacy, identify associated factors, and assess potential drug-drug interactions in pediatric prescribing.

Material and Methods: This was an academic, prospective, observational and cross-sectional study. Ethical clearance was obtained, and a sample size of 117 pediatric patients was determined based on existing prevalence rates. Data collection involved reviewing treatment records and conducting personal interviews, focusing on socio-demographic profiles, symptoms, and drug therapy. Polypharmacy was defined as the simultaneous use of two or more different medications, and potential drug-drug interactions were assessed using the Drug Interaction Checker by Medscape.

Results: Analysis of 117 pediatric patients revealed a high prevalence of polypharmacy (93.16%), with the majority prescribed 3-4 drugs concurrently. Potential drug-drug interactions were observed in 14% of prescriptions, primarily categorized as „Monitor Closely”. Albuterol and xylometazoline emerged as the most common drug pair associated with moderate pDDIs. Multivariate logistic regression identified polypharmacy as a significant predictor for pDDIs ($p < 0.00017$), while age, gender, and weight showed no significant associations.

Conclusion: The study underscores the significant prevalence of pediatric polypharmacy and potential drug-drug interactions, highlighting the need for improved prescribing practices and medication safety measures in pediatric care. Addressing these concerns requires ongoing research and development efforts to enhance therapeutic efficacy and safety for pediatric patients.

Keywords: Pediatric Polypharmacy, Potential Drug-Drug Interactions, Predictive Factors, Medication Safety

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INTRODUCTION

Use of medicinal drugs revolves around a balance between advantages of symptom alleviation or disease modification, which enhances quality or duration of life and the potential for short- and long-term adverse effects [1]. This leads to uncertainty regarding net health outcomes associated with various medication combinations which is further augmented in the care of children for whom there is a lack of safety checks. Regardless of uncertainty, use of drugs is on the rise in the pediatric population [2].

„Pediatric polypharmacy” is defined as the use of two or more different medications at the same time for more than one day [3,4]. The prevalence of chronic diseases in children has steadily increased during the last five decades [5]. Polypharmacy is on the rise in the goal of treating such complicated and many co-morbidities, which fosters potential drug-drug interactions (PDDI), adverse drug reactions (ADRs), and increased medical costs [6,7].

Unlike the elderly, few studies on pediatric polypharmacy have been conducted. According to a review of pediatric polypharmacy prevalence, Asia had the highest median prevalence of 45.4 percent, while North America had the lowest median prevalence of 30.4 percent [8]. Both inpatient and outpatient pediatric patients suffer from polypharmacy. As a result of the polypharmacy, PDDIs and ADRs occur, posing a risk to children's health. In an Indian prospective observational study, 64.81 percent of adverse drug reactions (ADRs) were reported in patients using multiple drugs [9]. Another clinical study, performed in pediatric intensive care unit patients, has found 75 percent of patients taking several medications were exposed to at least one PDDI, regardless of severity [10].

According to the United Nations International Children's Emergency Fund (UNICEF), India has 67,385 newborns born every day, accounting for one-sixth of all child births worldwide [11]. Chronic medical conditions will become more common as the number of children grows, potentially leading to polypharmacy. There is still a possibility of a knowledge gap in pediatric polypharmacy, which motivates us to do this research.

AIM

The aims of the study were:

1. To estimate prevalence of polypharmacy based on the number of medications prescribed in pediatrics OPD.
2. To identify factors associated with polypharmacy in the pediatric population.
3. To identify potential drug-drug interaction in pediatric prescribing.

MATERIAL AND METHODS

Type of study: This was an academic, prospective, observational and cross-sectional study.

Site: Department of Pharmacology and Department of Pediatrics, GMERS Medical College and Hospital, Gandhinagar. **Study Duration:** April 2022 to June 2022. **Ethical Clearance:** The study protocol was presented in the Institutional Ethics Committee (IEC), GMERS Medical College and Hospital, Gandhinagar. The study protocol was approved by IEC (No.: GMERS/MCG/IEC/09/2022).

Sample Size: According to a review of pediatric polypharmacy prevalence, Asia had the highest median prevalence of 45.4 percent.[8] Considering this prevalence of polypharmacy (~45%) the sample size calculated is 95.

Inclusion Criteria: The study included pediatric patients (age <18 years) of both genders who visited the Pediatrics outpatient department (OPD) for consultation or who were referred from other departments. **Exclusion Criteria:** There were no specific exclusion criteria.

Collection of Data: Patients who met the inclusion criteria were included in the study. Patients were included in the study on a pro rata basis, and all patients and their parents were informed about the study's objective and nature in a language they can understand. Before inclusion in the study, written informed consent was obtained from all patients and their parents. All the data needed to meet the objectives were gathered by reviewing the patients' treatment records and by conducting personal interviews with each study participant. These data were recorded on the case record form (CRF). The CRF contained information about the patient's socio-demographic profile, including current symptoms, drug therapy, and other relevant details.

Polypharmacy: As such, there is no

accepted definition for polypharmacy as per the number of drugs prescribed simultaneously. According to online literature, „pediatric polypharmacy” is defined as the use of two or more different medications at the same time for more than one day.[3,4] So, for the present study, a prescription with two or more different medications will be considered polypharmacy.

Potential drug-drug interactions (pDDI): Potential drug-drug interactions were assessed using computer-based checks online on the internet (Drug Interaction Checker by Medscape).[12] According to the website pDDI will be categorized for all drugs prescribed in a prescription as follows:

- Minor: Minimally clinically significant. Clinical relevance of the interaction is unlikely.
- Monitor Closely: Moderately clinically significant. Use it only under special circumstances or when close monitoring is required.
- Serious - Use Alternative: Highly clinically

significant. Combinations should be avoided since the risk of an interaction outweighs the benefit.

- Contraindicated: Drug pairs should not be used concurrently.

Statistical Analysis: The data were collected using google form and entered into Microsoft Excel. The data were analyzed using RStudio and tables were created using the package. Qualitative variables were described using the absolute (n) and relative (%) frequencies. Comparisons among subgroups were performed using Fisher's exact test. The current study also aimed to identify predictors of potential drug-drug interactions (pDDIs) through the application of multivariate logistic regression analysis. A statistically significant correlation has been identified between polypharmacy and potential drug-drug interactions (pDDI) ($p < 0.00017$). Age, gender, and the number of prescribed fixed-dose combinations (FDCs) do not demonstrate a significant association with pDDI.

Table 1. Distribution of patients according to age

Age	Patients, n (%)
<1 year	28 (24%)
1-4 years	37 (32%)
5-9 years	31 (26%)
10-14 years	20 (17%)
15-17 years	1 (0.9%)
Mean Age (years)	4.7±4.3

Table 2. Distribution of Patients according to gender

Age	Female, n (%)	Male, n (%)
<1 year	10 (21%)	18 (26%)
1-4 years	17 (35%)	20 (29%)
5-9 years	14 (29%)	17 (25%)
10-14 years	6 (13%)	14 (20%)
15-17 years	1 (2.1%)	0 (0%)
Total	48 (41.02%)	69 (58.97%)
Mean Age	4.5±3.8	4.9±4.7

Table 3. Number of Drugs Prescribed

Number of drugs	Patients, n (%)
1	8 (6.8%)
2	24 (21%)
3-4	62 (53%)
5-9	23 (20%)

Table 4. Number of pDDI among all the patients

Number of pDDI	Patients, n(%)
0	93 (79%)
1-2	16 (14%)
3-5	6 (5.1%)
≥6	2 (1.7%)

pDDI - Potential drug-drug interaction

RESULTS

A total of 117 pediatric (age ≤ 18 years) patients, who met selection criteria, were included in the study. The majority of the patients belonged to the age group of 1-4 years with mean age of 4.7±4.3 (Table 1) and were male (58.97%) (Table 2).

On analysis of prescription of the patients, a total of 109 patients (93.16%) were prescribed ≥2 drugs simultaneously out of which the highest number of patients - 62 (53%) - received 3-4 drugs, while 23 (20%) were given > 5 drugs (Table 3).

The pDDIs were evaluated using the Drug Interaction Checker by Medscape [12]. All the drugs prescribed were entered into the online checker for assessing the pDDIs for each prescription. It was found that 93 (79%) prescriptions did not have any pDDIs Out of 24 (20.8%) prescriptions with pDDIs male 16 (14%), prescriptions, 6 (5.1%) prescriptions, 2 (1.7%) prescriptions had 1-2 pDDIs, 3-5 pDDIs, ≥6 pDDIs, respectively (Table 4). On classifying pDDIs based on their severity there were 59 (95%) pDDIs which were Monitor Closely, 2 (3.22%) Serious pDDIs and 1(1.61%) minor pDDIs (Table 5). Co-prescription of albuterol and xylometazoline has been found out to be the most common drug pair involved in Moderate pDDIs.

Age	Female n (%)	Male n (%)	Total n (%)	p-value*
Monitor Closely	16 (28%)	43 (44%)	59 (95%)	0.051
Minor	1 (1.8%)	0 (0%)	1 (1.61%)	0.4
Serious - Use Alternative	0 (0%)	2 (2.0%)	2 (3.22%)	0.5
Total	17	45	62	

Table 5. Distribution of pDDI based on severity

pDDI - Potential drug-drug interaction

* - Pearson's Chi-squared test; Fisher's exact test

Drugs pairs	No. of pDDI	Effect of drug interaction
albuterol + xylometazoline	24	Both increase sympathetic (adrenergic) effects, including increased blood pressure and heart rate. Also, both decrease sedation.
chlorpheniramine + xylometazoline	12	Chlorpheniramine increases and xylometazoline decreases sedation. Effect of interaction is not clear, use caution.
chlorpheniramine + albuterol	8	Chlorpheniramine increases and albuterol decreases sedation. Effect of interaction is not clear, use caution.
phenylephrine + xylometazoline	6	Both increase sympathetic (adrenergic) effects, including increased blood pressure and heart rate. Also, both decrease sedation.
albuterol + phenylephrine	4	Both increase sympathetic (adrenergic) effects, including increased blood pressure and heart rate. Also, both decrease sedation.
albuterol + azithromycin	3	Both increase the QTc interval.
pantoprazole + ferrous sulfate	1	Pantoprazole will decrease the level or effect of ferrous sulfate by increasing gastric pH
metronidazole + acetaminophen	1	Metronidazole will increase the level or effect of acetaminophen by affecting hepatic enzyme CYP2E1 metabolism.
potassium chloride + albuterol	1	Potassium chloride increases and albuterol decreases serum potassium. Effect of interaction is not clear, use caution.
azithromycin + cetirizine	1	Azithromycin will increase the level or effect of cetirizine by P-glycoprotein (MDR1) efflux transporter.
domperidone + acetaminophen	1	The metabolism of domperidone can be decreased when combined with acetaminophen.

Table 6. Number of pDDI among all the patients

pDDI - Potential drug-drug interaction

Among all the patients studied, various drug pairs exhibited potential drug-drug interactions (pDDIs). The most prevalent interactions were observed between albuterol and xylometazoline, with 24 instances recorded, leading to an increase in sympathetic effects and decreased sedation. Chlorpheniramine combined with xylometazoline resulted in 12 pDDIs, showing conflicting effects on sedation. Additionally, interactions between pantoprazole and ferrous sulfate, metronidazole and acetaminophen, and potassium chloride and albuterol each occurred once, showcasing diverse effects on drug levels or physiological parameters. These findings emphasize the importance of monitoring and caution when prescribing medications to mitigate potential

adverse outcomes [table 6].

In the present study we also tried to find predictors of pDDIs using multivariate logistic regression analysis (Table 7). The statistically significant association has been found between the polypharmacy and pDDIs (< 0.00017). Age, gender, and weight do not show significant association with pDDIs.

DISCUSSION

The study included prescriptions from 117 subjects who attended Pediatric OPD. With an increasing number of pediatric age groups and also chronic conditions among them [5,11], polypharmacy becomes prevalent [6]. With this background study was conducted to assess

Variables	Coefficients	Standard Error	t Stat	P-value
Gender	-0.06753	0.072652	-0.92954	0.354608
Age (years)	0.001662	0.019864	0.083695	0.933449
Weight (kg)	0.002496	0.007467	0.334318	0.738765
Number of drugs	0.096901	0.024868	3.896545	0.000167*

Table 7. pDDI and associated factors

pDDI - Potential drug-drug interaction

* - p-value <0.01: Highly significant association

Table 9. Categories of potential drug-drug interactions

Categories	Clinical Implication
Minor	Minimally clinically significant. The clinical relevance of the interaction is unlikely.
Monitor Closely	Moderately clinically significant. Use it only under special circumstances or when close monitoring is required.
Serious	Highly clinically significant. Use Alternative. Combinations should be avoided since the risk of an interaction outweighs the benefit.
Contraindicated	Drug pairs should not be used concurrently

prevalence and predictive factors of pediatric polypharmacy and potential drug drug interaction.

The term „Polypharmacy” has many discrepancies in its definition. However, the majority of studies investigating polypharmacy rely on the textual definition that hinges on the quantity of prescribed medications [13,14] of more than 2 medications for children with or without specifying duration [3]. On analysis of prescriptions, polypharmacy (prescriptions of ≥ 2 drugs) has been found in 109 prescriptions (93.16 %). The mean number of drugs prescribed was 3.46.

Previous study has shown that patients who are subjected to polypharmacy are also exposed to multiple pDDIs [10]. In the present study out of 117 prescriptions 16 (14%) have 1 - 2 PDDI, 6 (5.1%) have 3 - 5 PDDIs and 2 (1.7%) have ≥ 6 PDDIs. Based on severity, out of 62 PDDIs were categorized as „Minor” (1.61%), „Monitor Closely” (95%), „Serious-Use Alternative” (3.22%). The most common was „Monitor Closely” which is 95%.

Apart from financial burden, there are many negative outcomes of polypharmacy, such as pDDI. ADRs are one of the crucial public health problems in the pediatric population which causes an increase in drug induced- morbidity and mortality inspite of efforts being made in reducing incidence of ADRs [9]. Our study shows a strong association between polypharmacy and pDDIs (p- Value = 0.00017) similarly to other studies. Polypharmacy along with additive risk of pDDI is also an important predictor of ADR [15–19]. Study shows that among infants who are administered more than 10 drugs, 60% experience at least one adverse drug reaction (ADR) [15].

Most common pDDI was between albuterol and xylometazoline in which both the drugs decrease sedation. Most serious pDDI in our study was between albuterol and azithromycin in which both drugs increase QTc interval. Clinicians often overlook the pediatric population as being at significant risk for drug-

drug interactions (DDIs) and polypharmacy, typically associating these issues with critically ill or older patients. However, some children with chronic conditions require medications across various drug classes, putting them at equal or greater risk for adverse drug reactions (ADRs) compared to adults [20]. Limited data and FDA labeling for pediatric use lead to the extrapolation of adult drug efficacy and safety results, resulting in „off-label” prescribing [21]. Predicting potential drug-drug interactions in children is challenging due to their dynamic development and immature organ systems responsible for drug metabolism. So, Potential drug-drug interactions in children are inferred from adult data, but the precision of predicting DDIs is impacted by an extra array of patient factors unique to pediatrics [22,23].

Polypharmacy is increasingly common in managing chronic pediatric conditions, justified by treatment guidelines for certain conditions but lacking evidence-based guidance for others [24]. As children transition into adolescence, the risk of DDIs becomes more related to the combinations of medications prescribed. Certain patient groups, such as adolescent girls, those from low-income households, foster care, or with disabilities, are more prone to psychotropic polypharmacy. Factors like episodic healthcare, inconsistent insurance coverage, and lack of pDDI information on over-the-counter product labels contribute to inappropriate drug combinations [25].

Predictive factors for pediatric polypharmacy include chronic medical conditions, comorbidity, psychiatric disorders, medication side effects, caregiver polypharmacy, access to healthcare, prescribing practices, parental preferences, drug interactions, and treatment failure. Research suggests that polypharmacy in pediatric patients is prevalent, especially among those with life-limiting conditions, and warrants further investigation [3,26]. While some factors like gender and diagnosis may not significantly predict polypharmacy, others such as the number and duration of medica-

tions, appropriateness, and clinical setting are important considerations [26]. Additionally, socioeconomic status and parental beliefs influence polypharmacy rates. Collaborative efforts among healthcare professionals are crucial for optimizing medication regimens and improving outcomes for pediatric patients [27]. Further research is needed to explore these factors comprehensively and develop tailored interventions to mitigate polypharmacy risks in children.

CONCLUSION

In this study, we focused on general polypharmacy in pediatric patients which revealed prevalence of polypharmacy to be 93.16% as per definition for pediatric population. The current study's results indicate that pediatric patients face a potential threat of prescription polypharmacy due to the existence of comorbidities. Approximately 14% of the examined prescriptions exhibit at least one potential drug-drug interaction (pDDIs). Furthermore, the research highlights polypharmacy as a significant predictor for pDDIs. Employing rational prescribing practices and leveraging information technology can be beneficial in enhancing medication safety for vulnerable populations, such as geriatric patients. The area of pediatric polypharmacy requires further development and research around adverse and long-term effects of multiple medications. Additionally, research to promote effective yet safer therapy for the pediatric population.

STRENGTHS AND LIMITATIONS

The research provides a robust sample size of 117 pediatric patients, ensuring a comprehensive dataset for analysis and enhancing the reliability of the findings. Furthermore, the study utilizes a systematic approach to evaluate potential drug-drug interactions (pDDIs). The detailed analysis of pDDIs, including their prevalence, severity, and specific drug pairs involved, offers valuable insights into the complex interactions between medications, contributing to a deeper understanding of pediatric polypharmacy. Moreover, the research incorporates multivariate logistic regression analysis to identify predictors of pDDIs, providing a sophisticated statistical approach to discern factors influencing the occurrence of interactions, thereby enhancing the depth of

the study's findings.

Despite the strengths, the study may have limited generalizability as it was conducted in a specific pediatric outpatient setting, potentially restricting the applicability of the findings to broader pediatric populations or different healthcare settings. Additionally, the reliance on prescription data may not fully capture actual medication adherence or patient outcomes, potentially introducing biases or discrepancies between prescribed and actual medication use.

Thus, pediatric polypharmacy and potential drug-drug interactions present significant challenges due to children's unique pharmacological characteristics, inadequate pediatric-specific drug data, and prevalent off-label prescribing. Clinicians must acknowledge these risks, particularly in chronically ill pediatric patients, and employ strategies like enhanced medication monitoring and patient/caregiver education to minimize adverse outcomes. Despite the theoretical nature of potential drug-drug interactions (pDDIs), healthcare practitioners must remain vigilant. Addressing these interactions requires comprehensive educational initiatives, although they can be time-intensive. Additionally, healthcare professionals may struggle to remember every potential drug interaction, given frequent changes in treatment regimens.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Polifarmacija i interakcije lekova u pedijatriji

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KRATAK SADRŽAJ

Uvod: Evidentna je rastuća zabrinutost u vezi polifarmacije u pedijatriji i potencijalnih interakcija lek- lek (pDDIs) u kontekstu pedijatrijske nege, gde preovladavaju nesigurnosti u pogledu kombinacija lekova i bezbednosnih provera. Uprkos sve većoj incidenci hroničnih bolesti među decom, postoje ograničena istraživanja o pedijatrijskoj polifarmaciji, sa različitim stopama prevalencije prijavljenih širom sveta.

Cilj: Cilj studije bio je da se proceni prevalencija polifarmacije, identifikuju povezani faktori i procene potencijalne interakcije lek-lek u pedijatrijskom propisivanju.

Materijal i metode: U studiji je korišćen prospektivni, opservacioni dizajn poprečnog preseka. Dobijeno je etičko odobrenje, a veličina uzorka od 117 pedijatrijskih pacijenata je određena na osnovu postojećih stopa prevalencije. Prikupljanje podataka je uključivalo pregled evidencije lečenja i vođenje ličnih intervjua, fokusirajući se na socio-demografske profile, simptome i terapiju lekovima. Polifarmacija je definisana kao istovremena upotreba dva ili više različitih lekova, a potencijalne interakcije lek-lek su procenjene korišćenjem Medscape-a za proveru interakcije lekova.

Rezultati: Analiza 117 pedijatrijskih pacijenata pokazala je visoku prevalenciju polifarmacije (93,16%), pri čemu je većina istovremeno prepisivala 3-4 leka. Potencijalne interakcije između lekova primećene su u 14% recepata, prvenstveno kategorisanih kao „Pažljivo nadgledajte”. Albuterol i ksilometazolin su se pojavili kao najčešći par lekova povezan sa umerenim pDDI. Multivarijantna logistička regresija je identifikovala polifarmaciju kao značajan prediktor za pDDI ($p < 0,00017$), dok starost, pol i težina nisu pokazali značajnu povezanost.

Zaključak: Studija naglašava značajnu prevalenciju pedijatrijske polifarmacije i potencijalne interakcije medikamenta i leka, naglašavajući potrebu za poboljšanom praksom propisivanja i merama bezbednosti lekova u pedijatrijskoj nezi. Rešavanje ovih problema zahteva stalna istraživanja i razvojne napore kako bi se poboljšala terapijska efikasnost i bezbednost za pedijatrijske pacijente.

Ključne reči: polifarmacija u pedijatriji, potencijalne interakcije između lekova, prediktivni faktori, bezbednost lekova

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