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Variation of the Prevalence of Pediatric Polypharmacy: A Scoping Review

Courtney Baker, MS¹, James A. Feinstein, MD, MPH², Xuan Ma, MS¹, Shari Bolen, MD, MPH^{3,4}, Neal V. Dawson, MD^{3,4}, Negar Golchin, Pharm. D, MPH⁵, Alexis Horace, Pharm. D, BCACP⁶, Lawrence C. Kleinman, MD, MPH⁷, Sharon B. Meropol, MD, MSCE, PhD^{7,8}, Elia M. Pestana Knight, MD⁹, Almut G. Winterstein, PhD¹⁰, and Paul M. Bakaki, MD, PhD¹

¹Department of Population & Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH,

²Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO,

³Center for Health Care Research and Policy, MetroHealth, Cleveland, OH,

⁴Department of Medicine, MetroHealth Medical Center, Cleveland, OH,

⁵School of Pharmacy, University of Washington, Seattle, WA,

⁶Department of Clinical Sciences, University of Louisiana at Monroe College of Pharmacy, Monroe, LA,

⁷UH Rainbow The Center for Child Health and Policy, University Hospitals, Cleveland, OH and School of Medicine, Case Western Reserve University, Cleveland, OH,

⁸Department of Pediatrics, Case Western Reserve University School of Medicine,

⁹Epilepsy Center/Neurological Institute, Cleveland Clinic, Cleveland, OH,

¹⁰Department of Pharmaceutical Outcomes and Policy and Department of Epidemiology, University of Florida, Gainesville, FL.

Abstract

Corresponding Author: Paul M. Bakaki, MD, PhD, **Address:** Case Western Reserve University, 10900 Euclid Ave, Cleveland, OH 44106, pmb18@case.edu.

Authorship:

Dr. Bakaki conceptualized and designed the study; collected, synthesized, and interpreted data; drafted the initial manuscript; and revised the manuscript for intellectual content.

Dr. Feinstein conceptualized and designed the study; synthesized, and interpreted data; drafted the initial manuscript; and revised the manuscript for intellectual content.

Ms. Baker and Ms. Ma collected, synthesized, and interpreted data; drafted the initial manuscript; and revised the manuscript for intellectual content.

Dr. Golchin and Dr. Horace conceptualized and designed the study; collected, synthesized, and interpreted data; and revised the manuscript for intellectual content.

Dr. Dawson, Dr. Kleinman, Dr. Winterstein, Dr. Bolen, Dr. Pestana Knight, and Dr. Meropol conceptualized and designed the study; synthesized and interpreted data; and revised the manuscript for intellectual content.

All authors approved the final version of manuscript as submitted for publication, and they agree to be accountable for all aspects of the work.

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Purpose: To examine the range of prevalence of pediatric polypharmacy in literature through a scoping review, focusing on factors that contribute to its heterogeneity in order to improve the design and reporting of quality improvement, pharmacovigilance, and research studies.

Methods: We searched Ovid Medline, PubMed, EMBASE, CINAHL, Ovid PsycINFO, Cochrane CENTRAL, and Web of Science Core Collection databases for studies with concepts of children and polypharmacy, along with a hand search of the bibliographies of six reviews and thirty included studies. We extracted information regarding study design, disease conditions, and prevalence of polypharmacy.

Results: Two hundred eighty-four studies reported prevalence of polypharmacy. They were more likely to be conducted in North America (37.7%), published after 2010 (44.4%), cross-sectional (67.3%), in outpatient settings (59.5%). Prevalence ranged from 0.9% to 98.4%, median 39.7% (interquartile range [IQR] 22.0%–54.0%). Studies from Asia reported the highest median prevalence of 45.4% (IQR 27.3%–61.0%) while studies from North America reported the lowest median prevalence of 30.4% (IQR 14.7%–50.2%). Prevalence decreased over time: median 45.6% before 2001, 38.1% during 2001–2010, and 34% during 2011–2017. Studies involving children under 12 years had a higher median prevalence (46.9%) than adolescent studies (33.7%). Inpatient setting studies had a higher median prevalence (50.3%) than studies in outpatient settings (38.8%). Community level samples, higher number and duration of medications defining polypharmacy, and psychotropic medications were associated with lower prevalence.

Conclusions: The prevalence of pediatric polypharmacy are high and variable. Studies reporting pediatric polypharmacy should account for context, design, polypharmacy definition, and medications evaluated.

Keywords

polypharmacy; polytherapy; prevalence; child; adolescent; pediatric

INTRODUCTION

Pediatric polypharmacy is the term used to describe children taking more than one medication.^{1,2} Literature has shown that the prevalence of polypharmacy is on the rise for both adults and children.^{3,4} While the full implications of polypharmacy are unknown, polypharmacy has been linked to an increase in adverse drug reactions⁵, potential drug-drug interactions⁶, hospital readmissions⁷, and medical costs.⁸ The observed prevalence of pediatric polypharmacy depends on patient characteristics, contextual, and study design factors. However, the definition of polypharmacy often varies across studies due to the nature of the study question, clinical context, population studied, and the subsequent study design, making it difficult to compare the prevalence of polypharmacy across studies. Identifying factors which contribute to the discrepancies in the prevalence of polypharmacy is an important step towards creating a consistent set of methodological approaches to accurately measure pediatric polypharmacy and to subsequently design interventions to safely manage polypharmacy in children.

A variety of factors influence the observed prevalence of pediatric polypharmacy. Previous studies have examined various aspects of polypharmacy that affect its prevalence including

the length of medication overlap and study setting.^{9,10} For example, hospitalized patients are particularly at risk of experiencing high polypharmacy levels compared to non-hospitalized patients;¹¹ and also, they are at high risk of adverse events related to polypharmacy. Even among non-hospitalized individuals, whether the population studied is in a clinical or community setting, has a significant impact on the prevalence of reported polypharmacy.^{12,13} The few existing studies that focus on specific medication classes responsible for pediatric polypharmacy are mainly concerned with psychotropic medications. Therefore, a gap exists when assessing the overall prevalence of polypharmacy in children or the prevalence in other pharmacological groups.^{9,10,14} Furthermore, ambiguity in the definition of pediatric polypharmacy leaves more potential for imprecision in prevalence estimates. Pediatric polypharmacy prevalence can also vary by age, sex, duration of polypharmacy, and calendar time.^{3,15}

Thus, there exists a significant potential for discrepancies in the prevalence of pediatric polypharmacy that may not always be accounted for in studies. We conducted a scoping review to investigate the magnitude and heterogeneity of the prevalence of pediatric polypharmacy. We aimed to, firstly, quantify the prevalence of pediatric polypharmacy in published literature and, secondly, identify factors, e.g. study population, geographic region, clinical setting, and definition of polypharmacy, that contribute to the heterogeneity of the prevalence, in order to provide guidance for designing and reporting on aspects of pediatric polypharmacy in future research.

METHODS

We briefly describe the methods of our study, details of which have been published¹⁶. The framework for this scoping review was based on the design by Arksey and O'Malley with enhancements from others.^{17–23} A scoping review is a knowledge synthesis approach that addresses an exploratory research question to establish key concepts, types of evidence, and gaps in research related to a field.¹⁸ The method included specifying a research question, identifying potentially relevant studies, identifying qualifying studies, extracting relevant information, and summarizing and analyzing the information.

The search strategy included both free text and controlled vocabulary for the concepts of polypharmacy and children. The original search was conducted in October 2016 and updated in July 2017. The eight databases searched were Ovid Medline, PubMed, EMBASE, CINAHL, Ovid PsycINFO, Cochrane CENTRAL, ProQuest Dissertations & Theses A&I, and the Web of Science Core Collection. The PsycINFO search strategy is shown in Figure 1. A hand search was conducted of the bibliographies of six relevant review articles and thirty randomly selected included studies as well.

Studies were selected if they included a definition, or assessment of polypharmacy in children 0–21 year of age as an aim, outcome, predictor, or covariate. Reviews, clinical trials, case series, case reports, conference abstracts, letters, comments, and opinion pieces were excluded. Additional exclusion criteria included polypharmacy during pregnancy or breastfeeding, not differentiating between adults and children, and not written in English. Studies in which polypharmacy prevalence was not reported or could not be computed were

also excluded (e.g. case control studies). Consistent with scoping review methodology, we did not assess study quality.¹⁷ Each study was assessed by two reviewers separately for inclusion using standardized forms to apply similar criteria during two phases: title/abstract and full text screening. Disagreements were solved either through consensus by both reviewers or brought to the full group of nine reviewers for discussion.

Information was extracted regarding: study characteristics including design, year of publication, country, and clinical setting of the research; disease conditions; definition of polypharmacy including number of medications, duration of concurrence of medications, whether it was assessed at drug or class level, and whether concurrently or sequentially taken; and prevalence of polypharmacy or mean number of medications. We computed polypharmacy prevalence when all the necessary information was available and prevalence was not reported. Our definition of polypharmacy for this calculation was two or more medications irrespective of duration,²⁴ when a study did not offer a definition. The data extraction was completed by one reviewer and checked by a secondary reviewer for accuracy.

We examined the distribution of the prevalence of polypharmacy or mean number of medications using non-parametric statistical methods. We computed the overall and variable level-specific median, first and third quartiles, as well as the minimum and maximum of the prevalence and mean number of medications. We compared median prevalence or median of the means among levels of variables of interest using the Kruskal-Wallis test at a statistical significance level of $\alpha < 0.05$. EPPI Reviewer 4²⁵ was used for creating screening and extraction forms, assigning studies to reviewers, double screening studies, reconciling differences, data cleaning and report generation. Data analysis was conducted using R software.²⁶

RESULTS

Summary of Included Studies

We identified and screened 4,398 titles, which resulted in 363 qualifying studies for review and data extraction under the whole research project. Of the 363 studies, for this analysis, we excluded 10 where everyone was on polypharmacy by design, 37 that did not report overall prevalence or mean number of medications, and 4 that were case control studies. Our final sample was 312 studies: 250 reported only prevalence, 28 reported only mean number of medications, and 34 reported both (Figure 2).

The distribution of characteristics of the 284 (250+34) studies that estimated overall prevalence is shown in Table 1. The studies were predominantly conducted in North America (37.7%, $n=107$), published in 2011 or later (44.4%, $n=126$), cross-sectional by design (67.3 % $n=191$), and predominantly used primary data (50.4%, $n=143$) in outpatient settings (59.5% $n=169$). Most studies included both children and adolescents (67.6%, $n=192$), and were conducted in populations that used at least one medication (73.9%, $n=210$). About 90% of the studies ($n=258$) defined polypharmacy as two or more medications. While most studies did not report number of days with overlapping medications (68.3%, $n=194$), when reported, 1–30 days was the most frequent interval

(13.4%, n=38). Most studies evaluated polypharmacy at the level of individual drugs (81.7%, n=232) rather than class level. Epilepsy (46.1%, n=131) and central nervous system agents (antiepileptic) (52.8%, n=150) were the most commonly studied disease conditions and medications, respectively.

Prevalence of Polypharmacy

As shown in Figure 3, prevalence of pediatric polypharmacy was highly variable, ranging from 0.9% to 98.4%. The median prevalence (interquartile range) was 39.7% (22.0% - 54.0%). Detailed information about studies that had extreme (less than 5th percentile or greater than 95th percentile) prevalence is shown in Supplementary Table 1. Studies reporting extremely low prevalence of polypharmacy were more likely to be large community-level studies conducted in the US or more likely to include individuals not on any medications than studies reporting extremely high prevalence.^{27–40} Additionally, studies reporting low prevalence were more likely to evaluate polypharmacy at the drug class level, sequentially, use overlapping periods longer than 30 days, or evaluate psychotropic medications compared to those with extremely high prevalence. On the other hand, studies reporting extremely high prevalence of polypharmacy were likely to be conducted in Asia, in inpatient settings, use overlapping periods less than 31 days, or assess polypharmacy in multiple complex chronic conditions, or multiple medication classes.^{5,24,41–52}

Table 2 shows the median, first, and third quartiles of the prevalence of pediatric polypharmacy in relation to different characteristics. Concerning continent, studies conducted in Asia had the highest median prevalence of 45.4% (IQR 27.3%–61.0%) while studies conducted in North America had the lowest median prevalence of 30.4% (14.7%–50.2%), $p<.05$. There has been a steady decline in pediatric polypharmacy over the last three decades (45.6%, 38.1%, 34.0%, $p<.01$) (Table 2 and Supplementary Table 2).

With respect to study design, prospective cohort studies had the highest median prevalence of 49.1% (29.4%–61.7%) while retrospective cohort studies had the lowest median prevalence of 33.8% (18.6%–52.4%), $p<.05$. Studies using electronic health records (46.8%, 31.5%–75.0%), chart review (45.8, 30.7%–57.9%), and primary data collection (43.6%, 26.7%–55.0%) had higher overall prevalence than studies using other data sources, with insurance claims and drug registry-based studies reporting the lowest prevalence of 17.5, $p<.01$. Inpatient studies had a higher median prevalence than outpatient studies of 50.3% (27.4%–64.2%) and 38.8% (21.9%–50.6%), respectively, $p<.05$. Studies focused on under-12-year-old children had higher median prevalence of 46.9% than studies focused on adolescents only, which had a median prevalence of 33.7%, $p<.01$.

The median prevalence of polypharmacy in populations using at least one medication was much higher than that of the general population (43.4% vs 27.1%), $p<.001$. Studies that defined polypharmacy with 1–30 overlap days had a higher median prevalence than those with >30 overlap days (37.2% vs 23.8%), but both were lower than the overall median prevalence. Studies that focused on sequential (over an interval with/without overlapping medications) polypharmacy had the lowest median prevalence of polypharmacy (19.8%) compared to studies that defined polypharmacy as greater than or equal to two medications (39.7%), or greater than or equal to three or four or five medications (25.4%), though not

statistically significantly different. The median prevalence of drug level polypharmacy (42.1%) was higher than that of class level polypharmacy (23.0%), $p < .01$. Studies that evaluated polypharmacy in epilepsy (42.0%) or other somatic disease (45.4%) had a higher median prevalence of polypharmacy than studies that evaluated it in psychiatry conditions (27.5%), $p < .05$. Regarding medications, the highest median prevalence of polypharmacy was observed in studies evaluating non-psychotropic central nervous system agents (42.1%) while studies of psychotropic agents had the lowest median prevalence of polypharmacy of 27.5%, $p < .001$.

Mean Number of Medications

Table 3 shows medians, first and third quartiles of the mean number of medications. Sixty-two studies reported mean number of medications as a measure of polypharmacy with an overall median (IQR) of 3.0 (2.2–4.7). Of the 62 studies, 34 studies also reported prevalence while 28 reported only mean number of medications. Retrospective cohort studies (3.1 [2.4–6.4]) and cross-sectional studies (3.1 [2.3–4.3]) reported higher mean number of medications than prospective cohort studies (2.1 [1.6–5.0]). Studies conducted among inpatients reported higher mean number of medications compared to those conducted among outpatients, 4.1 (3.3–7.4) and 2.6 (1.4–3.4) respectively, $p < .01$. Studies focusing on children only (3.7 [3.2–5.7]) had higher mean number of medications than studies focusing on adolescents only (1.9 [1.7–2.2]) or studies focusing on children and adolescents (2.4 [1.6–3.4]), $p < .05$. Studies that defined polypharmacy as sequential (6.1 [3.5–8.6]) reported higher mean number of medications than those up to 30 days of concurrent polypharmacy (2.8 [2.3–4.5]), $p < .01$. Studies of polypharmacy in somatic diseases reported higher mean number of medications (3.7 [3.1–5.7]) than those of psychiatric (2.3 [2.1–3.1]) or epilepsy (1.8 [1.4–2.6]) disease conditions, $p < .01$.

The studies that reported a mean number of medications without overall prevalence identified a higher number of medications than those that reported both a mean number of medications and prevalence (4.5 vs. 2.4) (Supplementary Table 3). Additionally, they were conducted mostly in inpatient settings, including neonatal intensive care units (NICUs). Eight out of 12 NICU studies reported mean number of medications without reporting prevalence of polypharmacy. Other characteristics of studies that reported a mean number of medications without reporting prevalence included evaluating multiple drugs/classes and being in international settings (Supplementary Table 3).^{1,3,53–74} Supplementary Table also shows the rest of the studies that reported prevalence or average number of medications.

DISCUSSION

Using the scoping review research methods, we found the prevalence of pediatric polypharmacy varying by study setting, methodology, medications, or diseases evaluated. The prevalence of pediatric polypharmacy, although highly differing across studies, had a median of 40%, interquartile range 22% - 54%. We found studies done in Asia, published before the year 2000, or conducted in the inpatient settings to have median prevalence higher than 45%. On the other hand, studies conducted in North America, or published in 2011 or later had median prevalence less than 35%. Study methodology, including design, data

sources, population, age group, and definition of polypharmacy had a great impact on the observed prevalence of polypharmacy. Highest median prevalence of polypharmacy was observed in prospective cohort studies, chart reviews, those conducted among children 12 years of age or younger, or among populations using at least one medication. The lowest median prevalence was found in retrospective cohort studies, studies using insurance claims or drug registries, studies assessing sequential or class-level polypharmacy, or in studies defining polypharmacy as at least 3 or 4 or 5 medications. The majority of studies that reported drug-level information focused on central nervous system medications, specifically psychotropic and antiepileptic medications.

Consistent with a study that reviewed global trends of antipsychotic polypharmacy by region, we found the overall prevalence of pediatric polypharmacy lowest in North America¹⁴, mainly due to low prevalence of psychotropic polypharmacy (Supplementary Table 4). Contrary to the findings of this systematic review, our review observed a decrease in the prevalence of pediatric polypharmacy over the last three decades, again explained by a decrease in psychotropic polypharmacy. The decrease in pediatric psychotropic polypharmacy over decades may be explained by concerns raised about adverse effects associated with second generation antipsychotics whose use soared when they were introduced in the 1990s.^{75,76} The apparent trend of reduction in polypharmacy prevalence over time found in this study appears to result from efforts towards reducing second generation antipsychotics use following the initial increase.^{77–79}

We found that children had higher prevalence of all-drug polypharmacy than adolescents, but upon stratification on medication category, our findings were consistent with those of researchers who have demonstrated higher prevalence of psychotropic polypharmacy among adolescents groups.^{16,45} The overall median average number of medications also supports this as children under 12 years had a higher median of the mean number of medications than adolescents. It is important to consider age groups when assessing pediatric polypharmacy in order to acknowledge the inconsistency of prevalence of polypharmacy by age.

In order to design future quality improvement and pharmacovigilance strategies, more consistent methodologic approaches are required. The majority of studies were cross-sectional in nature, but this may not adequately capture and describe the duration of risk that longitudinal studies would. Furthermore, few studies assessed combinations of medicines or reported days of overlap. This is particularly problematic when trying to assess concurrent polypharmacy and the potential for drug-drug interactions. Future pediatric polypharmacy studies that evaluate the spectrum of medications a child is taking over time should address this limitation. The healthcare setting has a great impact on the prevalence of polypharmacy as demonstrated in our study and should be considered when designing pediatric polypharmacy studies. Hospitalized children are exposed to multiple medications over a short period. Whether studies reported prevalence of polypharmacy or mean number of medications, the inpatient setting had the highest magnitude of polypharmacy.

Although central nervous system drugs represent a class of medications with higher potential for causing adverse drug events, pediatric patients—especially those with more complex chronic conditions—rely on a variety of other classes of medications. In order to fully

understand the prevalence and consequences of polypharmacy in this more fragile population, polypharmacy studies will need to examine the full spectrum of medications to which children are exposed, including medication categories with known potential for interactions, such as pain, cardiovascular, and endocrinological medications.

Our study had several strengths and limitations. The scoping review methodology resulted in inclusion of a large number of studies conducted using different methods in a variety of settings, enabling us to assess prevalence of polypharmacy in different subgroups. However, due to the heterogeneity of the studies, measures of central tendency such as mean or median, without a measure of spread, were imperfect metrics to summarize our findings. We thus urge researchers to consider reporting the median prevalence of pediatric polypharmacy and the interquartile range. More focused designs, such as systematic reviews, should be considered when addressing specific questions in order to limit the heterogeneity in the prevalence of polypharmacy associated with scoping reviews.

To explain heterogeneity in the prevalence of pediatric polypharmacy research and generate comparable findings, researchers in this field should clearly and precisely measure and report on factors that are associated with the highest variability in prevalence. The population studied should be well defined in terms of age, study setting, and whether it is at community or health facility level (inpatient or outpatient). Polypharmacy should be well defined, and it should be stated if polypharmacy is limited to a specific pharmacological category or disease. These measurements should supplement the traditional methods including study design, data sources, and sample size to yield constructive findings that will advance the field of pediatric polypharmacy.

In conclusion, pediatric polypharmacy is prevalent and varies according to patient populations, research methodology, or medications studied. Researchers need to define specific aspects of the patient population, such as age group and clinical setting; research design, such as definition of polypharmacy, longitudinal, or cross-sectional design; and medication categories evaluated in order for the prevalence of pediatric polypharmacy to be better characterized and comparable across studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points:

The prevalence of pediatric polypharmacy is highly variable in terms of patient population, study design, and medications.

The prevalence was high in inpatient settings, among children less than 12 years old, when the studies were conducted in Asia, or electronic health records were used.

It decreased with time from before 2001 to 2017, and it was low in population-based studies and when psychotropic medications were studied.

In order to better understand the magnitude of polypharmacy, researchers should design longitudinal studies, and account for context, polypharmacy definition, and medications studied.

PsycINFO <1806 to July Week 1 2017> Search Strategy:

-
- 1 exp POLYPHARMACY/ (970)
 - 2 ((prescribe* or prescription*) adj10 multiple drug*).ti,ab,id. (22)
 - 3 (hyperpolypharmacy or hyper-polypharmacy or hyper polypharmacy or polypharmacy or poly-pharmacy or poly pharmacy or polytherapy or poly-therapy or poly therapy or poly-medication or polymedication or poly medication or multiple medication* or multiple prescription* or combination pharmacotherapy).ti,ab,id. (2477)
 - 4 1 or 2 or 3 (2746)
 - 5 limit 4 to (100 childhood <birth to age 12 yrs> or 200 adolescence <age 13 to 17 yrs>) (376)
 - 6 (child* or infant* or neonate* or toddler* or adolescent* or teen* or pediatric* or paediatric* or school or boy* or girl* or baby or babies or newborn* or juvenile* or minors).ti,ab,id. (1007883)
 - 7 4 and 6 (382)
 - 8 5 or 7 (509)

Figure 1:
PsychoINFO Search Strategy

Figure 2: Flow Diagram of Studies Identified, Screened, and Extracted, PRISMA 2009

Studies that estimated prevalence and those that estimated mean number of medications are not mutually exclusive. Two hundred and fifty studies reported prevalence only, 28 studies reported mean number of medications only, and 34 studies reported both mean and prevalence.

Figure 3:
Distribution of Overall Prevalence of Pediatric Polypharmacy

Table 1:

Characteristics of Included Studies

Characteristic	Number of Studies	Percentage
Overall	284	100%
Continent		
Africa	18	6.3%
Asia	73	25.7%
Europe	72	25.4%
North America	107	37.7%
Oceania	4	1.4%
South America	9	3.2%
Combinations	1	0.4%
Year of Publication		
Up to 2000	55	19.4%
2001–2010	103	36.3%
2011–2017	126	44.4%
Study Design		
Cross Sectional	191	67.3%
Prospective Cohort	38	13.4%
Retrospective Cohort	55	19.4%
Data Sources		
Primary Data Collection	143	50.4%
Chart Review	59	20.8%
Insurance Claims	34	12.0%
Electronic Records	13	4.6%
Drug Registry	13	4.6%
Others & Combinations	22	7.7%
Sample Size		
13–99	90	31.7%
100–499	116	40.8%
500–999	12	4.2%
1000+	61	21.5%
Not Reported	5	1.8%
Age Categories		
Children Only (0–12)	34	12.0%
Adolescents Only (12–25)	14	4.9%
Children & Adolescents	192	67.6%
Not Reported	44	15.5%
Sex Percentage		
Mostly Boys (>50%)	176	62.0%

Characteristic	Number of Studies	Percentage
Mostly Girls (50%)	50	17.6%
Not Reported	58	20.4%
Polypharmacy Role		
Outcome	102	35.9%
Main Predictor	102	35.9%
Covariate	80	28.2%
Healthcare Setting		
Outpatient	169	59.5%
Inpatient	37	13.0%
Inpatient & Outpatient	22	7.7%
Others	47	16.5%
Not reported	9	3.2%
Prevalence Denominator		
Population using medications	210	73.9%
Population use/not use medications	74	26.1%
Number of Days Overlap		
1–30	38	13.4%
31–365+	28	9.9%
Sequent	24	8.5%
Not Reported	194	68.3%
Number of Medications Overlap		
>=2 Medications	258	90.8%
>=3/4/5 Medications	20	7.0%
Not Reported	6	2.1%
Polypharmacy Level		
Class level	35	12.3%
Drug level	232	81.7%
Combinations	17	6.0%
Pharmacological Category		
CNS Agents	150	52.8%
Psychotropic Agents	75	26.4%
Combination	55	19.4%
Not Reported	4	1.4%
Disease Condition		
Epilepsy	131	46.1%
Psychiatric	59	20.8%
Somatic	19	6.7%
Combinations	46	16.2%
Not Reported	29	10.2%

CNS = Central Nervous System

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Table 2:

Median & Interquartile Range of the Prevalence of Pediatric Polypharmacy by Study Characteristics

Characteristic	Median Prevalence	IQR
Overall	39.7	22.0 – 54.0
Continent *		
Africa	37.2	31.7 – 61.1
Asia	45.4	27.3 – 61.0
Europe	36.0	24.9 – 54.7
North America	30.4	14.7 – 50.2
Oceania	53.8	45.5 – 59.8
South America	38.8	25.8 – 43.8
Combinations	40.6	40.6 – 40.6
Year of Publication **		
Up to 2000	45.6	36.4 – 58.1
2001–2010	38.1	20.2 – 53.2
2011–2017	34.0	21.8 – 49.6
Study Design *		
Cross Sectional	38.0	22.4 – 51.4
Prospective Cohort	49.1	29.4 – 61.7
Retrospective Cohort	33.8	18.6 – 52.4
Data Sources ***		
Primary Data Collection	43.6	26.7 – 55.0
Chart Review	45.8	30.7 – 57.9
Insurance Claims	17.5	6.6 – 32.9
Electronic Records	46.8	31.5 – 75.0
Drug Registry	17.5	12.0 – 42.3
Others & Combinations	28.0	21.6 – 48.2
Sample Size ***		
13–99	44.2	33.1 – 51.7
100–499	42.8	25.5 – 61.4
500–999	27.5	19.0 – 36.1
1000+	22.0	9.0 – 42.3
Not Reported	29.6	6.6 – 45.6
Age Categories **		
Children Only (0–12)	46.9	35.3 – 68.5
Adolescents Only (12–25)	33.7	18.9 – 51.3
Children & Adolescents	39.1	21.6 – 52.2
Not Reported	33.2	18.0 – 51.6
Sex Percentage		

Characteristic	Median Prevalence	IQR
Mostly Boys (>50%)	40.4	26.0 – 52.2
Mostly Girls (50%)	35.6	20.1 – 60.7
Not Reported	37.4	17.7 – 54.4
Polypharmacy Role ***		
Outcome	27.3	13.1 – 50.2
Main Predictor	45.0	28.8 – 57.1
Covariate	42.2	26.9 – 52.5
Healthcare Setting *		
Outpatient	38.8	21.9 – 50.6
Inpatient	50.3	27.4 – 64.2
Inpatient & Outpatient	32.6	29.2 – 50.5
Others	27.5	14.0 – 50.5
Not reported	45.5	34.7 – 57.4
Prevalence Denominator ***		
Population using medications	43.4	26.7 – 57.4
Population use/not use medications	27.1	16.1 – 44.4
Number of Days Overlap ***		
1–30	37.2	25.4 – 49.6
31–365+	23.8	6.9 – 36.2
Sequent	19.8	11.3 – 35.9
Not Reported	43.7	26.8 – 57.2
Number of Medications Overlap		
>=2 Medications	39.7	24.1 – 53.7
>=3/4/5 Medications	25.4	12.1 – 51.6
Not Reported	54.1	15.0 – 76.9
Polypharmacy Level **		
Class level	23.0	11.8 – 38.6
Drug level	42.1	26.0 – 54.9
Combinations	42.0	26.0 – 55.5
Pharmacological Category ***		
CNS Agents	42.1	27.4 – 54.5
Psychotropic Agents	24.9	11.7 – 44.6
Combination	45.4	23.4 – 68.0
Not Reported	43.7	34.4 – 57.2
Disease Condition *		
Epilepsy	42.0	27.3 – 54.4
Psychiatric	27.5	11.4 – 49.9
Somatic	45.4	31.2 – 64.1

Characteristic	Median Prevalence	IQR
Combinations	32.7	22.3 – 52.1
Not Reported	42.3	14.0 – 63.3

CNS = Central Nervous System

IQR=Interquartile Range

*
p-value<0.05

**
p-value<0.01

p-value<0.001

Table 3:

Median and Interquartile Range of the Average Number of Medications by Study and Population Characteristics.

Characteristic	Median of Mean Number of Medications	Interquartile Range of Mean	Number of Studies (%)
Overall	3.0	2.2 – 4.7	62 (100.0%)
Continent			
Africa	3.1	2.6 – 3.7	6 (9.7%)
Asia	3.1	2.1 – 3.7	17 (27.4%)
Europe	2.4	1.5 – 5.3	8 (12.9%)
North America	2.4	2.2 – 3.7	22 (35.5%)
Oceania	4.9	3.0 – 6.7	2 (3.2%)
South America	6.3	3.9 – 7.6	7 (11.3%)
Year of Publication			
Up to 2000	5.7	4.3 – 7.2	2 (3.2%)
2001–2010	2.8	2.3 – 4.7	30 (48.4%)
2011–2017	3.1	2.0 – 4.0	30 (48.4%)
Study Design			
Cross Sectional	3.1	2.3 – 4.3	43 (69.4%)
Prospective Cohort	2.1	1.6 – 5.0	11 (17.7%)
Retrospective Cohort	3.1	2.4 – 6.4	8 (12.9%)
Data Sources			
Primary Data	2.8	1.8 – 4.0	26 (41.9%)
Chart Review	3.6	2.4 – 5.7	21 (33.9%)
Insurance Claims	5.6	3.5 – 5.7	3 (4.8%)
Electronic Records	6.0	3.0 – 9.1	4 (6.5%)
Drug Registry	2.9	2.7 – 3.2	2 (3.2%)
Other	2.2	1.6 – 2.3	6 (9.7%)
Healthcare Setting**			
Outpatient	2.6	1.4 – 3.4	24 (38.7%)
Inpatient	4.1	3.3 – 7.4	23 (37.1%)
Inpatient & Outpatient	2.3	1.7 – 4.8	10 (16.1%)
Others	2.4	2.3 – 2.5	5 (8.1%)
Age Categories**			
Children Only (0–12)	3.7	3.2 – 5.7	26 (41.9%)
Adolescents Only (13–17)	1.9	1.7 – 2.2	3 (4.8%)
Children & Adolescents	2.4	1.6 – 3.4	25 (40.3%)
Not Reported	2.4	1.6 – 3.3	8 (12.9%)
Population***			
Not Reported	4.8	3.6 – 8.5	25 (40.3%)

Characteristic	Median of Mean Number of Medications	Interquartile Range of Mean	Number of Studies (%)
Population Using Medications	2.4	1.4 – 3.0	26 (41.9%)
General Population	2.4	2.1 – 3.1	11 (17.7%)
No. of Overlap Days**			
1–30	2.8	2.3 – 4.5	12 (19.4%)
31–365+	2.2	1.7 – 3.9	3 (4.8%)
Sequential	6.1	3.5 – 8.6	14 (22.6%)
Not Reported	2.5	1.7 – 3.6	33 (53.2%)
No. of Overlapping Medications***			
>=2 Medications	2.3	1.7 – 3.0	31 (50.0%)
>=3/5/4 Medications	2.4	2.3 – 3.1	5 (8.1%)
Not Reported	4.5	3.5 – 8.0	26 (41.9%)
Polypharmacy Level			
Class level	3.2	2.2 – 4.4	3 (4.8%)
Drug level	2.9	2.2 – 4.2	52 (83.9%)
Combinations	3.7	2.2 – 5.4	7 (11.3%)
Pharmacological Category***			
CNS Agents	1.6	1.4 – 2.5	10 (16.1%)
Psychotropic Agents	2.3	1.9 – 2.4	12 (19.4%)
Combination	3.7	3.1 – 6.3	36 (58.1%)
Not Reported	2.5	2.1 – 2.7	4 (6.5%)
Disease Condition**			
Epilepsy	1.8	1.4 – 2.6	8 (12.9%)
Psychiatric	2.3	2.1 – 3.1	12 (19.4%)
Somatic	3.7	3.1 – 5.7	13 (21.0%)
Combination	2.1	1.5 – 2.4	7 (11.3%)
Not Reported	3.6	2.6 – 5.0	22 (35.5%)

CNS=Central nervous system

* p-value<0.05

** p-value<0.01

*** p-value<0.001