Prescribing patterns of polypharmacy in Korean pediatric patients

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Abstract

Background
Several studies have examined the risk and health outcomes related to polypharmacy among the elderly. However, information regarding polypharmacy among pediatric patients is lacking.

Objective
The aim of this study was to investigate the prevalence of polypharmacy and its related factors among the pediatric population of South Korea.

Methods
We used national claim data from the Health Insurance Review and Assessment Service—Pediatric Patients Sample (HIRA-PPS) in Korea originating from 2012 through 2016. Polypharmacy was defined as a daily average of two or more drugs used yearly. Complex chronic conditions (CCCs) were examined to evaluate concomitant chronic diseases in pediatric patients. Age-specific contraindications and potential drug-drug interactions were assessed according to criteria established by the Korea Institute of Drug Safety & Risk Management (KIDS). Descriptive statistics and logistic regression were conducted to analyze the status of polypharmacy and its associated risk factors in pediatric patients.

Results
The 5-year prevalence of pediatric polypharmacy in pediatric patients was 3.7%. The prevalence of polypharmacy was much higher in younger pediatric patients: 9.5% for patients between the ages of 1–7 years, 0.9% for ages 6–11 years, and 1.1% for ages 12–19 years. Pediatric patients with CCCs, Medical Aid benefits, or a hospital admission history had a significantly higher prevalence of polypharmacy when compared to their counterparts without those conditions. The most commonly prescribed drugs were respiratory agents (29%) followed by anti-allergic drugs (18.7%), central nervous system agents (15.9%), antibiotics (10.1%), and gastrointestinal drugs (7.7%). There was a positive correlation between the
daily average number of inappropriate prescriptions and the degree of polypharmacy, especially in pediatric patients between the ages of 1–7 years. Contraindications and potential drug-drug interactions occurred in 11.0% and 10.1% of patients exposed to polypharmacy, respectively.

**Conclusions**

One in ten pediatric patients under the age of 7 years was prescribed two or more concurrent drugs on average per day. Furthermore, pediatric patients exposed to polypharmacy showed an increased risk of inappropriate drug use. The implementation of a medication review system that considers pediatric patient polypharmacy exposure would reduce inappropriate drug use and prevent unwanted adverse outcomes.

**Introduction**

Polypharmacy is a common global phenomenon caused by increasing comorbidities [1, 2], and it increases the risk of inappropriate medicine use, drug-drug interactions, and adverse health outcomes [3–5]. Several polypharmacy studies have been conducted in many countries and most examine elderly populations [2]. Their results indicate that there is an association between polypharmacy and adverse health outcomes such as falls, hospitalization, and mortality [4, 5]. Concerns about polypharmacy in pediatric patients are on the rise [6] because of the increasing number of prescriptions used to treat chronic conditions in pediatric patients [7–9].

Very few studies are available regarding polypharmacy among pediatric patients, and they are limited to a single region (i.e. western countries) or a single drug class (i.e. antipsychotics) [10, 11]. Several studies have investigated polypharmacy exposure for a wide variety of medicines and their related outcomes based on population-level data [12, 13]. One study examining pediatric patients from 463 hospitals in the United States (U.S.) found that 10% of children less than one year of age received 11 medications on the first day of admission into a healthcare facility and were cumulatively exposed to 29 medications during 7 days of admission [12]. Another U.S. study by Feinstein et al. examining polypharmacy among outpatients reported that 35% of pediatric patients (N = 232,240) were exposed to more than two concurrent drugs for at least one day during the one-year observation period [13]. It also showed that the potential for drug-drug interactions increased as the number of drugs being prescribed increased [13]. However, there is a lack of information on pediatric polypharmacy for many drug classes in East Asia countries.

Polypharmacy is generally characterized as the use of multiple medications. However, accurately defining pediatric polypharmacy and quantify related exposures is challenging [14]. Some studies have defined polypharmacy based on the actual number of prescribed drugs [12, 13] while other studies have assessed polypharmacy using the average number of drugs prescribed [15, 16]. The method that uses the maximum number of concurrent drugs is sensitive when multiple drugs are used to treat acute illnesses; however, the method that uses an average number of drugs is useful for assessing long-term exposure to medicines used daily for the treatment of chronic conditions. As chronic diseases in pediatric patients increases, along with a tendency toward polypharmacy, the duration of drug exposure and the number of active ingredients in the drugs being prescribed should be carefully considered [17].
The objectives of this study were to investigate the prevalence of polypharmacy based on the daily average number of medications taken and to assess the risk factors associated with polypharmacy in pediatric patients in South Korea.

Materials and methods

Data source

We used the Health Insurance Review and Assessment Service–Pediatric Patients Sample (HIRA-PPS) claim database using data originating from 2012 through 2016. South Korea has a universal health coverage system consisting of the National Health Insurance Service (NHIS) and the Medical Aid Program, which covers approximately 97% and 3% of the Korean population, respectively. The HIRA manages and assesses claim data from NHIS and Medical Aid for 46 million patients (about 90% of the total population that visits medical institutions annually) that need to be reimbursed from approximately 80,000 health care centers per year. Data from 10% of all patients under the age of 20 were selected from the HIRA-PPS database using a random sampling of sex and age strata [18]. The HIRA-PPS also contains patient socio-demographic characteristics, medical treatment, prescription drug information, and disease diagnoses based on the International Classification of Diseases, 10th revision (ICD-10). We included patients only between the ages of 1–19 years (n = 977,817 from 2012, n = 906,556 from 2013, n = 967,193 from 2014, n = 945,550 from 2015, and n = 928,025 from 2016).

This study was approved by the institutional review board of Kyungpook University in September of 2018 (IRB Number KNU2018-0141).

Drug identification and classification

Medications were matched to their active ingredients using their nine-digit Korea Drug Code listed by the HIRA, and drug classifications were matched according to the Ministry of Food and Drug Safety (MFDS) (MFDS Internal Rule No. 68; 15 May 2015) [19].

Polypharmacy

Polypharmacy was defined as an average of two or more active ingredients per patient per day during the one-year observation period. To evaluate long-term exposure to polypharmacy, the average number of active ingredients was calculated on a yearly basis from January 1 through December 31. In this calculation, each active ingredient in a single combination drug was counted.

Complex chronic conditions

Complex chronic conditions (CCCs) were used to evaluate concomitant chronic diseases in pediatric patients. CCCs were categorized into nine groups: cardiovascular, respiratory, neuro-muscular, renal, gastrointestinal, hematologic or immunologic, metabolic, other congenital or genetic, and malignancy [20]. Additionally, we treated three prevalent chronic diseases that require long-term medication (asthma, psychiatric disease, and diabetes) in the same manner as CCCs.

Potential drug-drug interactions and age-related contraindicated drugs

Potential drug-drug interactions (PDDIs) and age-related contraindications were defined according to guidelines established by the Korea Institute of Drug Safety & Risk Management (KIDS) [21–23]. PDDIs and age-related contraindications defined by KIDS featured 954 drug pairs and 160 active ingredients, respectively. For analysis of PDDIs, we evaluated the list of
drugs prescribed on the same date and did not consider the prescription period. In the case of age-related contraindications, acetaminophen (sustained-release formulations), cetirizine, and levocetirizine, which were contraindicated due to their formulations rather than their ingredients, were excluded from the analysis.

Analysis

Descriptive statistics were used to demonstrate the overall prevalence of polypharmacy according to individual characteristics originating between 2012 and 2016. The associations between the presence of polypharmacy and the variables considered in this study (age, sex, insurance type, hospital admission, CCC categories, and the three other chronic diseases previously mentioned) were statistically tested via logistic regression. In these analyses, the presence of polypharmacy was the dependent variable, and the previously mentioned considered variables were the independent variables. Odds ratios and 95% confidence intervals are presented using multivariable logistic regression models. To assess the association between polypharmacy and inappropriate drug use, we analyzed the prevalence of age-related contraindications and PDDIs in the presence of polypharmacy. We performed chi-square tests to determine whether there was a significant difference in the proportion of inappropriate prescriptions between the polypharmacy and non-polypharmacy groups. We also investigated commonly prescribed drug classes in the pediatric polypharmacy group. For this analysis, the numerator of the proportion represented the sum of prescription days for each active ingredient according to the drug classification system of the MFDS. The denominator represented the sum of prescription days for all active ingredients used. Then, the proportions between the polypharmacy and non-polypharmacy groups were compared.

Stratified analysis was performed using age groups (patients aged 1–7 years, 8–13 years, and 14–19 years) due to the heterogeneity of comorbidities and prescription patterns. All analyses were performed using SAS 9.4 statistical software (SAS Inc., Cary, NC, USA).

Results

Table 1 shows the prevalence of polypharmacy by year, demographics, and chronic conditions. In pediatric patients, the 5-year prevalence (2012–2016) of polypharmacy was 3.7%. The overall prevalence of polypharmacy decreased with age: it was 9.5% for patients between the ages of 1–7 years, 0.9% for patients between the ages of 8–13 years, and 1.1% for patients between the ages of 14–19 years. A higher prevalence of polypharmacy was observed in pediatric patients with CCCs compared to those without CCCs. Patients with CCCs involving neurologic and neuromuscular diseases showed the highest prevalence of polypharmacy. Pediatric patients with other chronic conditions or any hospital admission history also had a higher prevalence of polypharmacy when compared with those without such conditions or history of hospital admission.

Multivariable logistic models showed that patients between the ages of 1–7 years have a seven times greater risk of polypharmacy than patients between the ages of 14–19 years after adjusting for chronic conditions and history of admission (OR = 7.14, 95% CI = 7.02–7.26). Also, pediatric patients with CCCs had a significantly increased risk of polypharmacy. The likelihood of polypharmacy due to chronic diseases was greater in patients between the ages of 8–19 years than in patients between the ages of 1–7 years. These patterns were prominent in patients with neurologic and neuromuscular CCCs and in patients with psychiatric disease. Pediatric patients with Medical Aid benefits (OR = 1.45, 95% CI = 1.40–1.49) or any admission history (OR = 2.68, 95% CI = 2.64–2.71) had a significantly higher risk of polypharmacy (Table 2).
Fig 1 shows the association between PDDIs and age-related contradictions in the presence of polypharmacy. The prevalence of inappropriate prescriptions was significantly higher for all age groups within the polypharmacy group. Among the three age groups, patients between the ages of 1–7 years showed the highest prevalence of PDDIs and age-related contradictions. Among patients between the ages of 1–7 years with polypharmacy exposure, approximately 10.1% and 11.0% had PDDIs and age-related contradictions in their medication use, respectively. The three most frequent PDDIs involved domperidone and clarithromycin, domperidone and mequitazine, and domperidone and metoclopramide. The three most frequently
prescribed drugs involved in age-related contradictions were mequitazine for patients younger than 24 months, loratadine for patients younger than 6 years, and thiocolchicoside/aescin for patients younger than 16 years.

Table 3 shows the prescription dosage for each drug class in the polypharmacy group. Regardless of age, respiratory agents were the most frequently administered drugs (29%),
followed by anti-allergic drugs (18.7%), central nervous system drugs (15.9%), antibiotics (10.1%), and gastrointestinal drugs (7.7%). However, the prescription pattern varied by age group. Among patients between the ages of 1–7 years with polypharmacy exposure, respiratory agents were most commonly prescribed (34.4%), followed by anti-allergic drugs (21.3%), and antibiotics (10.1%). Among patients between the ages of 8–19 years with polypharmacy exposure, the most frequently prescribed drug was a central nervous system drug that accounted for approximately half of all prescriptions (47.3% for ages 8–13 years and 49.0% for ages 14–19 years). Among central nervous system drug subclasses, antipsychotic drugs were prescribed most often (17.9% for ages 8–13 years and 22.5% for ages 14–19 years).

We also analyzed the prevalence of polypharmacy based on different calculation methods. We calculated the proportion of patients with a maximum number of prescribed drugs (0, 1–4, 5–9, and ≥10) for at least one day during the one-year observation period in 2016. The proportion of each exposure level was 2.9%, 16.5%, 71.9%, and 8.7%, respectively. This indicates that 80.6% of pediatric patients were prescribed more than five drugs concurrently on at least one day during the 1 year follow-up period (92.5% for ages 1–7 years, 76.3% for ages 8–13 years, and 72.9% for ages 14–19 years) (S1 Table).

Discussion

There have been inconsistencies in the definition of polypharmacy. Some studies qualified polypharmacy using terms such as duplication, drug-drug interaction, and non-match between medication and diagnosis, which confer a clinical meaning regarding inappropriate medication. However, most studies examining polypharmacy use the text definition that is based on the number of medications prescribed [2, 24]. The most commonly referenced number was more than 5 drugs for adults [2, 24] and more than 2 drugs for children [14]. In addition, the method for measuring polypharmacy exposure that considers the number of concurrent drugs prescribed is not standardized. The measurement that uses the maximum number of concurrently prescribed drugs per day, which is the most frequently used method, can provide intuitive information on the number of drugs used concurrently, but it is difficult to quantify the duration of medication. For example, children who were prescribed two drugs for only one day for one year would be considered exposed to polypharmacy [13]. Meanwhile, the calculation that relies on the daily average number of drugs prescribed has the advantage of providing both the number of medications prescribed and their duration. In this study, polypharmacy was defined and quantified as two or more active ingredients prescribed per day based on the daily average number of medications prescribed each year. Also, this study
focused on describing the long-term exposure of pediatric polypharmacy. Therefore, the daily average number of drugs prescribed was used to determine polypharmacy. This method is similar to the one described in the World Health Organization (WHO) guidelines on drug use indicators, stating that an average number of medications per prescription or patient greater than two is considered polypharmacy [25].

Our results show a higher prevalence of pediatric polypharmacy and age-related differences when compared to results from previous U.S. studies. Feinstein et al. graded pediatric polypharmacy exposure based on the maximum number of concurrent drugs prescribed (no medication, 0, 2–4, 5–9, and ≥10 drugs), and the proportion of each exposure level was 45.3%, 19.5%, 27.6%, 6.6%, and 1.0% of total samples, respectively [13]. However, our results were based on a daily average of ≥2 medications during the one-year observation period, making
direct comparisons with previous results difficult. Thus, to compare the results, we estimated the proportions of patients with a maximum number of prescription drugs for at least one day during the one-year observation period (0, 1–4, 5–9, and ≥ 10) using the same method as Feinstein et al. In summary, the proportions of patients with a maximum number of concurrent drugs ≥ 5 were 80.6% in our results and 7.6% in the U.S. study’s results. This indicates that pediatric polypharmacy exposure was more prevalent in South Korea than in the U.S. Despite the relatively high prevalence of polypharmacy, the prevalence of CCCs (5.1%) in South Korea was similar to that in the U.S. (5.9%) [12]. The rate of polypharmacy was higher in patients with CCCs or a hospital admission history than those without them, which was also in line with results from the previous U.S. study. However, age-related patterns of polypharmacy were different when compared to the previous U.S. study [12, 13]. Our results showed that polypharmacy prevalence was lower in patients between the ages of 14–19 years, whereas in the U.S. study, the prevalence was higher for the same age group [13].

Comparisons between nations regarding the prevalence of polypharmacy are difficult because health problems can vary between populations and comparable data is scarce. However, since the prevalence of chronic complex diseases was similar between Korea and the U.S., it is unlikely that differences in disease severity were associated with differences in the prevalence of polypharmacy. The greater utilization of healthcare in Korea might explain the relatively high polypharmacy prevalence and its different age-related patterns among pediatric patients. Korea reported the highest number of doctor visits per person (16.0 in 2015) among the 32 OECD countries (the average for OECD countries was 6.9 in 2015) [26]. In this context, the number of office visits per person was more than two times higher in patients between the ages of 1–4 years (27.4 per year) than in patients between the ages of 5–19 years (6.6–14.5 per year) in Korea [27]. However, among U.S. patients between the ages of 1–4 years (2.8 per year) and 5–14 years (2.0 per year), the values were nearly equivalent [28]. Thus, greater utilization of healthcare may have influenced the relatively high rates of polypharmacy, especially for younger children in Korea.

We found that the inappropriate prescription of drugs, including PDDIs and age-related contradictions, increased in pediatric patients with polypharmacy, which was consistent with previous studies [13, 29]. Moreover, the proportion of inappropriate drug prescriptions was notably highest in patients between the ages of 1–7 years among the three age groups. When considering the pharmacokinetic factors of pediatric patients, adverse drug reactions are greater in younger children. During the first decade of life, age-dependent changes in body composition and organ function are dynamic, and this leads to unpredictable pharmacokinetics [30]. For example, children have more body water than body fat when compared to adults, which affects the distribution of drugs. Drug metabolic enzymes such as cytochrome P-450 (CYP) isoforms and a glucuronosyltransferase (UGT) isoform are diminished in children. Thus, drugs are eliminated more slowly from the body, and drug concentrations may be increased. In addition, the structure and function of the gastrointestinal tract and kidney display age-dependent changes, and they are immature in early life [31].

In our study, the combination of antiemetic agents and antibiotics was the most frequently listed PDDI among pediatric patients. The medication selection and direction of treatment are determined by the clinical condition of the patient. However, evaluations of antiemetic agents and antibiotics may be helpful in reducing the potential harm of polypharmacy. In fact, the misuse of antiemetic agents and antibiotics has been specifically mentioned with the development of adverse drug events in pediatric patients [32–35]. In addition, we found that antipsychotic drugs were the major medication class prescribed to patients between the ages of 8–19 years with polypharmacy exposure. Previous studies have shown that the prevalence of psychotropic polypharmacy is substantial in pediatric patients [36, 37]. A study using the U.S.
National Ambulatory Medical Care Survey (2004–2007) reported that 32.2% of patients visiting medical facilities for mental disorder treatment were prescribed more than 2 classes of psychotropic medications [37]. The risk of ADEs and PPDIs increased with the number of antipsychotic medications prescribed [11, 29, 38].

Our study has several limitations. First, our overall study group did not include approximately 10% of the entire South Korean population that did not visit a clinic or hospital. Therefore, our prevalence of polypharmacy is limited to prescriptions provided to pediatric patients who visit a medical institution at least once during the one-year observation period. Second, we relied exclusively on the claim database, including prescriptions issued by the medical institute. Under this condition, we could not assess the patients’ compliance in taking the prescribed medication or the use of over the counter (OTC) medications. Thus, our polypharmacy prevalence results could be overestimated if patients did not take the medication even though they received the prescription. Also, our polypharmacy prevalence results could be underestimated if patients used additional OTC drugs. Third, we did not identify the appropriate indication for each medication. However, simply taking multiple medications at the same time could increase undesirable outcomes, including potential drug-drug interactions and prescription of contraindicated drugs [39, 40]. Lastly, a patient’s disease state was defined using ICD-10 codes provided by the database, and there is a possibility of uncertainties in the diagnosis.

Conclusions

Our study showed that several pediatric patients were exposed to polypharmacy that could result in inappropriate drug use. Health professionals, including pharmacists, need to be aware of this phenomenon and take action to reduce the number of medications that patients take. To aid in this, further evidence should be gathered so that pediatric medication guidelines can be established for the treatment of acute and chronic diseases. Furthermore, a system should be established to provide professional services that reduce polypharmacy exposure and prevent further unwanted outcomes in pediatric patients.

Supporting information

S1 Table. Prevalence of polypharmacy based on the maximum number of prescribed drugs for at least one day during the one-year observation period: PPS 2016.

(PDF)

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