Potential drug–drug interactions in pediatric outpatient prescriptions for newborns and infants

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\textbf{ABSTRACT}

Objectives: To surveyed the quantities, types, and related information of potential drug–drug interactions (DDIs) and estimate the off-label use percentage of pediatric outpatient prescriptions for newborns and infants from the National Health Insurance Research Database (NHIRD) of Taiwan.

Background: Adverse drug reactions (ADR) may cause morbidity and mortality, potential drug–drug interactions (DDI) increase the probability of ADR. Research on ADR and DDI in infants is of particular urgency and importance but the related profiles in these individuals are not well known.

Methods: All prescriptions written by physicians in 2000 were analyzed to identify potential DDIs among drugs appearing on the same prescription sheet.

Results: Of a total of 150.6 million prescription sheets, with 669.5 million prescriptions registered in the NHIRD of Taiwan, six million (3.99\%) prescription sheets were for 2.1 million infants with 19.4 million (2.85\%) prescriptions. There were 672,020 potential DDIs in this category, accounting for 3.53\% per prescription; an estimated one DDI in every three patients. The interactions between aspirin and aluminum/magnesium hydroxide were most common (4.42\%). Of the most significant drug–drug interactions, the interaction of digoxin with furosemide ranked first (20.14\%), followed by the interactions of cisapride with furosemide and erythromycin (6.02\% and 4.85\%, respectively). The interactions of acetaminophen and anti-cholinergic agents comprised most types of drug–drug interactions (6.62\%).

Conclusion: Although the prevalence rates of DDIs are low, life-threatening interactions may develop. Physicians must be reminded of the potential DDIs when prescribing medications for newborns and infants.

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1. Introduction

1.1. Background

Drug-drug interaction (DDI) is an important factor that may cause treatment failure or the development of side effects while the following adverse drug reaction (ADR) is major cause of increased mortality and morbidity. Fatal ADRs rank as the fourth to sixth leading causes of death in inpatients [1]. The death because of medical errors exceeded the number attributable to the eighth leading cause of death in the United States [2]. ADRs cause an estimated 5–6.5% of hospitalizations [1,3], and 2.5–4.4% of these originated from DDIs [4]. An estimated 1.46–35% outpatients may develop ADRs, and 13% of these cases may have serious drug reactions [5,6]. The findings of an investigation on DDIs using a sample database from the National Health Insurance Research Database (NHIRD) of Taiwan revealed the prevalence of potential DDIs to be 30%. Of all the potential DDI pairs, 9.9% of the pairs received a level 1 clinical significance classification, representing 3% of all prescriptions [7].

A systematic review of studies on ADRs in inpatient and outpatient children, and on ADRs causing hospital admissions indicated that the overall incidence of ADRs was 9.53% in inpatients, and severe reactions accounted for 12.29% of the total hospital admissions. The overall rate of pediatric hospital admissions due to ADRs was 2.09%. 39.3% of the ADRs causing hospital admissions were life-threatening reactions. In outpatient children the overall incidence of ADRs was 1.46% [6].

Not every healthcare provider can distinguish potential DDIs from ADRs, and take corrective measures accordingly. In a survey study, Glassman and his colleagues found that only 44% (ranging from 11 to 64%) of clinicians have correctly identified all drug–drug pairs [8]. A clinician’s understanding of DDI can decrease the likelihood of ADR, safeguard patient safety, and avoid associated medicolegal problems.

1.2. Drug interactions and off-label medication used in infant

Research on ADR and DDI in infants, children and adolescents is of particular urgency and importance because this vulnerable group displays developmental, physiological, and psychological differences from adults. However, the DDI profiles in these individuals are not well known because related studies are lacking. Newborns and infants are more susceptible to diseases therefore parents and healthcare providers usually pay more attention to this population. Knowledge of their DDI profiles is, therefore, necessary to avoid subsequent ADRs when prescribing medications.

Before any medicine is authorized for use in humans, the product must have undergone clinical trials to ensure that it is safe, of high quality, and effective. However, medicines may not have received the same trials for use in children due to ethical and economic issues. Therefore, few newly developed medications included clinical trials on pediatric populations, and there is an absence of suitable, authorized medicines for children’s use. As a consequence, the use of drugs outside the terms of the marketing authorization, known as off-label use, is quite common in pediatric pharmacotherapy. Studies have also revealed that the percentage of off-label drug use significantly associated with the risk of ADR [9,10].

The present study surveyed the quantities, types, and related information of prescriptions with potential DDIs for newborn and infant outpatients, and also evaluated off-label drug use related to DDI over a one year period.

2. Methods

2.1. Ethic statement

The confidentiality assurances were addressed by abiding the data regulations of the Bureau of National Health Insurance (BNHI), and institutional review board approval was waived.

2.2. Study population and National Health Insurance System in Taiwan

The population of Taiwan is 23,162,123 [11] with 23,074,487 insured by the National Health Insurance (NHI) program [12], a compulsory national health insurance system first implemented in 1995, and representing a nearly 99.6% enrollment rate. Several dozens of millions of health service claims are sent to the BNHI monthly where these undergo quality assurance checks by administrative staffs and are approved for payment under peer-review in a randomized sampling basis [13].

NHI claims for all prescriptions (including inpatients and outpatients) written by physicians (including general practitioners, specialists, dentists, and traditional Chinese physicians) are recorded in the National Health Insurance Research Database (NHIRD). A monthly updated NHI drug formulary forms the basis of reimbursements for hospitals and clinics, and over 21,000 pharmaceutical references have been validated by the Food and Drug Administration of the Department of Health. Due to redundancy of the pharmaceutical references, the lists of drugs have been re-classified according to the same formulations, regardless of the types of preparations. The revised drug formulary has 1600 pharmaceutical formulations. Healthcare facilities in Taiwan are classified into four types: medical centers, regional hospitals, local hospitals, and private practice clinics. They are defined by the scales, numbers of beds, and quality of medical and nursing care. For example, medical center should equip more than 500 beds with 22 clinical specialties while regional hospital should equip more than 250 beds. The categorizing task is managed by the Taiwan Joint Commission of Hospital Accreditation, a quasi-official body supported by the Department of Health of Executive Yuan of Taiwan. The rates of reimbursements differ due to the differing types of organizations which provide financial support to the hospitals.

The target study populations are newborns and infants. Newborns are those whose age younger than one month old while infants are age younger than 12 months old.
2.3. Drug interactions database

A drug interaction database was developed in which potential DDIs were defined according to the drug pairs in the Drug Interaction Facts, 2001 ed [14] and has been long-term used by Food and Drug Administration, Department of Health in Taiwan. The significance rating was determined according to onset, severity, and documentation of each DDI, using a scale of one to five. A rating of one is severe and well-documented, whereas a rating of five is unlikely and only partially or not documented (Table 1). Of 9328 drug interaction pairs, 1048 pairs are classified as significance level 1 and 3347 pairs as level 2.

2.4. Data analysis

The present study analyzed and identified prescription drugs with potential DDIs among drugs appearing on the same prescription sheet by cross-checking with the revised drug list and potential DDI database by applying Structured Query Language (SQL) procedure which can detect drug interaction in reasonable time even in real time fashion [15]. The SQL procedures were performed under MySQL v4.018 Database Server platform (Sun Microsystems, Santa Clara, CA, USA). Interactions involving two or more different dosages or frequencies of the same drug were excluded from the analyses.

The NHI prescriptions for newborns and infants written by all physicians during January 1 to December 31, 2000 were analyzed. The reason that we selected this period is the data set contained most complete nationwide prescriptions that were released earlier. The identifiable patient data were censored to ensure patient confidentiality. The following relevant data were extracted from each prescription sheet: patient ID, date of birth, clinic ID, facility type, prescribing physician ID, number of drugs, generic pharmaceutical ingredients regardless of the formulations (systemic or topical), and dispensing pharmacist ID. Drug interaction pairing, significance rating, severity level, documentation level, and DDI effects were generated from these data.

2.5. Off-label medication database

In the present study, a drug was considered off-label if it was prescribed to a child below the lowest approved age or outside of the age categories mentioned in the Summary of Product Characteristics, available in the Micromedex® database (Version 1.0, Thomson Reuters, New York, USA). There is no official regulatory definition of off-label medication use issued by BNHI, in order to unify the definition of off-label use, we referred Micromedex® as off-label database. The medications commit drug interactions were identified by this database.

2.6. Statistical analyses

Frequencies were used to present categorical variables and descriptive statistical analyses were performed using SPSS for Windows (Version 17.0, SPSS Inc, Chicago, Illinois, USA).

3. Results

In 2000, there were 150,560,023 prescription sheets (visits) with 669,449,835 prescriptions submitted to the BNHI. There were 6,001,066 (3.99%) prescription sheets with 19,047,078 (2.85%) prescriptions for total 2,151,455 newborns. The average of drugs per sheet was 3.17.

672,020 prescriptions had potential DDIs, representing 3.53% of the prescriptions in newborn infants and 11.20% of the prescription sheets; an estimated one DDI in every three patients. More than half of all DDIs were clinically irrelevant and negligible, with most significant interactions accounting for 5% of all DDIs. Tables 1 and 2 summarize the most frequent DDIs and relative percentages of significance levels.

Among DDIs with significance level 1 and major severity, the interactions between digoxin and furosemide were the most common (20.14%) (Table 3). Potential effects of these interactions are loop diuretic-induced electrolyte disturbances predisposing to digitalis-induced arrhythmias, possibly due to the increased urinary excretion of potassium and magnesium affecting cardiac muscle action. Despite the combination of loop diuretics and digitalis potentially resulting in cardiac arrhythmia, monitoring plasma levels of potassium and magnesium and providing supplements can avoid adverse events since this combination is essential in treating many cardiac diseases. The interactions of cisapride with furosemide and erythromycin were the following most significant interactions (6.02% and 4.85%, respectively).

The interactions of acetaminophen and anti-cholinergic agents comprised most classes of drug-drug interactions (6.62%), followed by the interactions of salicylates with non-steroidal anti-inflammatory drugs (NSAIDs) and antacids (5.40% and 4.46%, respectively) (Table 4).
DDIs occurred most frequently on prescriptions written by pediatricians (58.44%), followed by general practitioners (16.76%), and family doctors (6.81%) (Table 5).

Concerning the relationship between DDIs and organization types, most DDIs came from private clinics. However, more DDIs occurred in regional hospitals and medical centers (19.47% and 21.66% prevalence, respectively). The prevalence of DDIs occurring in private clinics was 1.25% (Fig. 1).

Off-label drug use also occurred among potential DDIs. Of the top 10 interactions pairs, off-label drug use accounted for 40%.

4. Discussion
The report, “To Err is Human”, published by the Institute of Medicine [2] highlighted patient safety issues. Elsewhere, the issue of improving medication safety is also regarded as an important goal in improving patient safety. Previous studies have well reviewed the problems of ADRs, and especially DDIs, in general medicine but few studies have evaluated ADRs in the pediatric field in recent years. Unlike ADRs, which are often unpredictable, by taking extra precautions when prescribing, physicians can avoid DDIs. The present study is considered the first large-scale investigation of potential DDIs of outpatient prescriptions in a nationwide population, including 2.1 million patients and with 19 million prescriptions for newborn and infants. The results show that 11.2% of visits will potentially develop DDIs; an estimated one DDI occurring in every three patients. Therefore, a high prevalence rate occurred in outpatient prescriptions for infants in comparison with the general population.

58% of all DDIs are clinically irrelevant and negligible (significance levels 4 and 5), with most significant interactions (level 1) accounting for only 5% of all DDIs. The interactions between aspirin and aluminum/magnesium hydroxide were most common (4.42%), with potential reducing effects on serum salicylate because antacid-induced increases in urinary pH reduce the renal reabsorption of salicylate, and thus increase salicylate clearance [14].

Table 2 – Top 10 drug–drug interactions and off-label use.

<table>
<thead>
<tr>
<th>Drug A</th>
<th>Drug B</th>
<th>Significance</th>
<th>N</th>
<th>%a</th>
<th>Overall %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Aluminum hydroxidec</td>
<td>3</td>
<td>18,700</td>
<td>2.78</td>
<td>0.08</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Aspirin</td>
<td>5</td>
<td>18,504</td>
<td>2.75</td>
<td>0.08</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Propranolol</td>
<td>5</td>
<td>13,054</td>
<td>1.94</td>
<td>0.06</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>Phenobarbital</td>
<td>2</td>
<td>11,786</td>
<td>1.75</td>
<td>0.05</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Phenobarbital</td>
<td>4</td>
<td>11,536</td>
<td>1.72</td>
<td>0.05</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Magnesium hydroxidec</td>
<td>3</td>
<td>10,999</td>
<td>1.64</td>
<td>0.05</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Ephedrinec</td>
<td>5</td>
<td>10,501</td>
<td>1.56</td>
<td>0.05</td>
</tr>
<tr>
<td>Ephedrinec</td>
<td>Phosphate Salts</td>
<td>3</td>
<td>10,115</td>
<td>1.51</td>
<td>0.04</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Aspirin</td>
<td>5</td>
<td>8791</td>
<td>1.31</td>
<td>0.04</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Acetaminophen</td>
<td>5</td>
<td>8253</td>
<td>1.23</td>
<td>0.04</td>
</tr>
</tbody>
</table>

a Total potential drug–drug interactions in newborn and infants: 672,020.  
b Total potential drug–drug interactions in general population: 22,812,747.  
c Off-label Use, Infant dosage is not available or advised in the summary of product characteristics in Micromedex® database.

Table 3 – Top 10 significance level 1 drug–drug interactions (total: 31,481).

<table>
<thead>
<tr>
<th>Drug A</th>
<th>Drug B</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>Furosemide</td>
<td>6339</td>
<td>20.14</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Furosemide</td>
<td>1894</td>
<td>6.02</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Erythromycin</td>
<td>1528</td>
<td>4.85</td>
</tr>
<tr>
<td>Isoniazide</td>
<td>Rifampin</td>
<td>1377</td>
<td>4.37</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Captopril</td>
<td>1069</td>
<td>3.40</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Prochlorperazinea</td>
<td>840</td>
<td>2.67</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Rifampin</td>
<td>764</td>
<td>2.43</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Furosemide</td>
<td>729</td>
<td>2.32</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Trichlormethiazine</td>
<td>727</td>
<td>2.31</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>Rifampin</td>
<td>717</td>
<td>2.28</td>
</tr>
</tbody>
</table>

a Off-label use, infant dosage is not available or advised in the summary of product characteristics in Micromedex® database.

Table 4 – Top 10 drug–drug interactions by drug class.

<table>
<thead>
<tr>
<th>Class A</th>
<th>Class B</th>
<th>Significance</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Anti-cholinergics</td>
<td>5</td>
<td>44,488</td>
<td>6.62</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Salicylates</td>
<td>5</td>
<td>36,303</td>
<td>5.40</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Antacids</td>
<td>3</td>
<td>29,940</td>
<td>4.46</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Salicylates</td>
<td>4</td>
<td>27,300</td>
<td>4.06</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Antacids</td>
<td>5</td>
<td>26,488</td>
<td>3.94</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Beta blockers</td>
<td>5</td>
<td>26,108</td>
<td>3.89</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Barbiturates</td>
<td>4</td>
<td>23,194</td>
<td>3.45</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>NSAIDs</td>
<td>2</td>
<td>21,188</td>
<td>3.15</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Aluminum salts</td>
<td>3</td>
<td>21,178</td>
<td>3.15</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Salicylates</td>
<td>4</td>
<td>18,365</td>
<td>2.73</td>
</tr>
</tbody>
</table>

a NSAIDs: non-steroid anti-inflammatory drugs.
There were few potentially life-threatening risks seen among all DDIs. Analysis of the most important DDIs ranked the interactions of digoxin first (33.25%), in significance level 1, followed by those of cisapride (23.6%). Reducing the dosage or carefully monitoring certain serum concentrations can avoid potential adverse drug events or reactions, but contraindications still exist. The most serious of these are the interactions of cisapride. Most interactions with cisapride result in severe cardiac toxicity such as QT prolongation, inducing dysrhythmia of Torsades de pointes, regardless of modification of dose. Although the United States withdrew cisapride from the market in July, 2000, it was still available for prescription in Taiwan at that time. Nowadays, physicians rarely use these drugs to treat patients. Another example is the interaction of isoniazide and rifampin (4.37%). Isoniazide and rifampin are commonly used for the treatment of tuberculosis, however, hepatic toxicity is possible with either agent and the risk may be increased when both are used concomitantly. Close monitoring liver function test and clinical symptoms of liver toxicity are necessary.

The interactions of antacids with salicylates and corticosteroids ranked third and fifth with respect to drug classes (Table 4). This may represent the prescribing behavior which favors antacids in Chinese culture.

### 4.1. Off-label drug use

Over 50% of the medicines used in children may not have been studied in this age group. In the European Union, the pediatric population (0–18 years) accounts for approximately 75 million people, representing 20% of the total population [16]. During October 1995 to September 2005, the European Agency for the Evaluation of Medicinal Products (EMEA) licensed 33% of all licensed active substances for use in children, 23% for use in infants, and 9% for use in newborns [17]. A review, involving 30 studies between 1985 and 2004, revealed that the overall rates of prescriptions considered off-label or unlicensed ranged from 11% to 80%, and identified higher rates in younger versus older patients [18]. A United States study showed that, in an outpatient setting, 62% of outpatient pediatric visits included off-label prescribing. Visits by children aged less than six years had a higher probability of including off-label prescribing (p < 0.01), especially visits by children aged less than one year (74% adjusted probability). Visits to specialists also involved a significantly increased probability (68% vs. 59% for general pediatricians, p < 0.01) of including off-label prescribing [19].

A nation-wide study, which included 2.19 million prescriptions to 968,465 children aged 0–18 years in Sweden during 2007, showed that physicians had prescribed 247 of the 386 substances (64%) included in the off-label analyses at least once, resulting in 295,000 off-label drug prescriptions, and constituting 13.5% of all dispensed prescriptions to children.

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**Fig. 1 – Relationship of prescriptions, drug–drug interactions, and facility type.**

**Table 5 – The top 10 types of practice (total: 672,020).**

<table>
<thead>
<tr>
<th>Department</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatrics</td>
<td>392,731</td>
<td>58.44</td>
</tr>
<tr>
<td>General practitioner</td>
<td>112,631</td>
<td>16.76</td>
</tr>
<tr>
<td>Family medicine</td>
<td>45,786</td>
<td>6.81</td>
</tr>
<tr>
<td>ENT</td>
<td>39,031</td>
<td>5.81</td>
</tr>
<tr>
<td>Emergent medicine</td>
<td>39,255</td>
<td>2.87</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>17,594</td>
<td>2.62</td>
</tr>
<tr>
<td>Surgery</td>
<td>7379</td>
<td>1.10</td>
</tr>
<tr>
<td>Dermatology</td>
<td>6343</td>
<td>0.94</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>5200</td>
<td>0.77</td>
</tr>
<tr>
<td>Gynecology</td>
<td>3643</td>
<td>0.50</td>
</tr>
<tr>
<td>Other specialties*</td>
<td>22,427</td>
<td>3.34</td>
</tr>
</tbody>
</table>

* Other specialties include orthopedics, plastic surgery, urology, neurosurgery, neurology, rehabilitation medicine, dentistry and psychiatry.
Clinical trials, especially those for this age group, may not have rigorously studied a number of drugs. This could potentially increase the risks of use in the pediatric population.

4.2. Off-label drug use and ADR

One study objectively evaluated the risk of ADRs and off-label drug use. This study involved 4455 drug prescriptions and more than 1000 admissions. ADRs associated with 112 (3.9%) of the 2881 licensed drug prescriptions and 95 (6%) of the 1574 unlicensed or off-label drug prescriptions. The number of medications administered simultaneously was associated with the risk of an ADR, but multivariate analysis showed no significant relationship between the use of unlicensed and off-label drugs and the risk of an ADR (relative risk [RR] 1.74, 95% CI 0.89–3.41, p < 0.106). The authors concluded that ADRs represent a significant problem following unlicensed or off-label drug prescriptions [9]. A French group identified the incidence of ADRs in an outpatient setting to be 1.41% (95% CI 0.79–2.11), while 42% of patients had received at least one off-label prescription. Off-label drug use significantly associated with ADRs (RR 3.44; 95% CI 1.26–9.38) [21]. Another Swedish group identified 112 patient-linked reports corresponding to 158 ADRs, of which 31% were serious. Antiasthmatic drugs were the suspected cause of almost every third adverse reaction. The average proportion of off-label drug prescribing amounted to 42.4% [22]. However, the studies involving ADRs and off-label drug use did not identify the incidence of DDI in ADR.

An UK study described the experiences with and attitudes toward pediatric off-label prescribing in primary care [23]. A prospective questionnaire survey among 202 general practitioners (GPs) identified that the most important sources of pediatric prescribing information were the British National Formulary (81%), personal experience (71%), and previous prescription notes (45%). Although the concept of off-label prescribing was familiar to 73.7% of GPs, over half (53.3%) were unaware that off-label prescribing is commonplace. These findings indicated that there is a significant lack of information concerning the extent and nature of off-label prescribing in primary care, and the possible ADRs arising from such prescriptions.

In the present study’s analyses of off-label drug use, three drugs (ephedrine, aluminum hydroxide and magnesium hydroxide) in four of the top 10 interactions represented 40% of off-label use. Only one drug (prochlorperazine) identified among the top 10 potential DDIs was significance level 1 (Tables 2 and 3).

Under the referral policy raised by government, patients with minor diseases will visit private clinics with lower co-payments so the majority of prescriptions came from private clinics in this study, but the highest prevalence of potential DDIs occurred in hospitals. High prevalence of potential DDIs in large-scale hospitals (medical centers and regional hospitals) was an expected finding. The complexity of the diseases in these hospitals which require more intensive care and multiple pharmacological treatments may account for this result. Pediatricians provided half of the prescriptions for newborns and infants, with other medical specialties also contributing potential DDIs. If physicians are not familiar with the pharmacological characteristics of the drugs they prescribe, their prescription, therefore, may potentially lead to the development of potential DDIs. As the electronic health records become more available, the medical activity scheme has been shifted from physician-oriented into patient-oriented, by which the medical records are centralized [24], and medication safety issues such as DDIs and medication redundancy could be improved [25]. Both national and local patient safety goals include reducing the occurrence of drug-related adverse events as an important task.

Previous evidences have revealed that computerized DDI screening systems could reduce the incidences of DDIs and ADEs [8,26,27]. In 2003, Bates et al. also suggested that the electronic medical records and computerized physician order entry systems which alert clinicians contributed to the decreased incidence of potential DDIs and related ADEs [28]. Therefore, to reduce the potential DDIs, large hospitals would benefit from making computerized drug interaction alerting or reminding systems [29]. Other decision support mechanisms can also reduce the medication frequency by personalized scheduling of complex prescriptions [30].

The findings of the present study should be interpreted with caution due to the following limitations. First, the study only focused on potential DDIs in outpatient prescriptions, and did not survey the real occurrence of DDIs and corresponding ADEs resulting from DDIs. Second, the methods did not include evaluation of some important factors which could contribute to ADEs with DDIs. These factors include body weight, genetics, co-morbidity, major organ function status, and drug compliance [31]. Third, the present assessed prescriptions on a single sheet, but not interactions with other medications prescribed on the other sheets of the same patient or during the same periods of time. Drug interactions may come from different visits or event across departments, potential interactions may occur if the overlap period of prescriptions is long enough, which will make prevalence increased. All generic pharmaceutical ingredients were taken as one regardless of formulations, which may have led to the over- or underestimation of potential DDIs. Furthermore, the definition of off-label use considered age, but not dose, indication/contraindication, formulation, and route and frequency of administration, which are also important factors when labeling a drug. These weaknesses suggest that the present study may have underestimated the prevalence of potential DDIs and off-label use in the study population. Future study on this research topic should consider addressing these study limitations. Finally, although the data used for analysis is nearly 10 years ago that characteristics of DDIs might change currently, however, the importance of this issue should be seriously explored and discussed in order to remind and strengthen clinicians’ awareness of the potential DDIs that might develop from their prescriptions.

5. Conclusion

Our analysis of a large-scale database in the present study increased understanding of the prevalence, significance levels, severity levels, and drug types of potential DDIs in outpatient prescriptions of newborn infants. Although the
prevalence rates of DDIs are low, life-threatening interactions may develop. Physicians and pediatricians need reminding of the potential DDIs when prescribing medications to newborns and infants.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

The conception and design of the study were raised by YCL; acquisition of data was done by YJC, MLY, YYT, PYW; analysis and interpretation of data were done by MLY, YJC, SJY, LJH; drafting the article was done by MLY; revising critically for important intellectual content was done by YCL, CYH; final approval of the version to be submitted was done by CYH.

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