Original Article

Prevalence and associated factors of drug-drug interactions in elderly outpatients in a tertiary care hospital: a cross-sectional study based on three databases

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Background: Drug-drug interactions (DDIs) are factors of adverse drug reactions and are more common in elderly patients. Identifying potential DDIs can prevent the related risks. Fewer studies of potential DDIs in prescribing for elderly patients in outpatient clinics. This study aimed to investigate the prevalence and associated factors with potential DDIs and potentially clinically significant DDIs (csDDIs) among elderly outpatients based on 3 DDIs databases.

Methods: A cross-sectional study was carried out on outpatients (≥65 years old) of a tertiary care hospital in China between January and March 2022. Patients' prescriptions, including at least 1 systemic drug, were consecutively collected. The potential DDIs were identified by Lexicomp®, Micromedex®, and DDInter. Patient-related clinical parameter recorded at the prescriptions and DDIs with higher risk rating was analyzed. Variables showing association in univariate analysis (P<0.2) were included in logistic regression analysis. Weighted kappa analysis was used to analyze the consistencies of different databases.

Results: A total of 19,991 elderly outpatients were involved in the study, among whom 21,527 drug combinations including 486 drugs occurred. Lexicomp®, Micromedex®, and DDInter respectively identified 32.22%, 32.93%, and 22.62% of patients have at least one potential DDIs, meanwhile, 9.16%, 14.53%, and 4.56% of patients have at least one potential csDDIs. Under any evaluation criteria, polypharmacy and neurology visits were risk factors for csDDIs. Lexicomp® has the highest coverage rate (87.86%) for drugs. Micromedex® identified the most csDDIs (740 drug combinations). Drugs used in diabetes and psycholeptics were frequently found in the csDDIs of 2 commercial databases. The consistency between Lexicomp® and Micromedex® was moderate (weighted kappa 0.473). DDInter had fair consistencies with the other databases.

Conclusions: This study showed the prevalence of potential DDIs is high in elderly outpatients and potential csDDIs were prevalent. Considering the relative risk, pre-warning of potential DDIs before outpatient prescribing is necessary. As the consistencies among identification criteria are not good, more research is needed to focus on actual adverse outcomes to promote accurate prevention of csDDIs.

Keywords: Drug-drug interactions (DDIs); elderly; outpatient; prevalence

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Introduction

A drug-drug interaction (DDI) can be defined as 1 drug's effect on another (1). The interaction mechanism may be roughly classified into pharmacokinetic and pharmacodynamic. DDIs may increase efficacy, decrease efficacy, or increase toxicity. As a primary type of drug-related problems (DRPs), some clinically significant DDIs (csDDIs) are associated with clinically adverse outcomes, such as adverse drug reactions (ADRs), readmission, and death (2-6). The elderly population is more vulnerable to the adverse effects of DDIs due to the coexistence of multiple diseases, the prevalence of polypharmacy, and age-related pharmacokinetic and pharmacodynamic changes (1,7). Epidemiological study of DDIs shows that older patients are more likely to be exposed to csDDIs (8). DDIs are somewhat predictable when clinical evidence is available and pharmacological effects are known. Identifying and preventing csDDIs is necessary to optimize pharmacotherapeutic outcomes in the elderly.

The prevalence of potential DDIs in elderly with multimorbidity in primary care varies 20–100% (9). A system review shows that the weighted mean prevalence of severe DDI was in rank order: hospital 28.9%, primary care 4.4%, and nursing home 3.3% (10). In prescriptions containing ≥2 medications belonging to elderly outpatients at least one clinically relevant DDI was detected in 61.7% (11). There is less data on potential DDIs and csDDIs in multiple prescriptions for elderly outpatients.

Highlight box

Key findings

- The prevalence of potential csDDIs in elderly outpatients ranged from 4.56% to 14.53%.

What is known and what is new?

- Fair consistency of Lexicomp® and Micromedex® in other populations and some drug classes and the prevalence of potential DDIs in single prescriptions for outpatient geriatric patients is known.
- This manuscript adds: (I) the prevalence of potential csDDIs and the consistency of Lexicomp® and Micromedex® in elderly outpatients; (II) the factors associated with potential csDDIs identified in multiple databases; (III) the trends of DDIs in outpatients under different combination cycles

What is the implication, and what should change now?

- More research on the risk and actual adverse outcomes of csDDIs is needed.

Factors contributing to the occurrence of DDIs in populations are varied in different researches, such as age, comorbidities, polypharmacy, nutritional status, and genetic constitution of an individual (8,12,13), comparison between studies is not straightforward as a result of differences DDI detections. Potential DDIs in clinical practice can be identified via drug instructions, pharmacy guidebooks, consensus lists, clinical decision support systems (CDSS), and electronic databases. CDSS can implement pre-event risk identification for prescriptions instead of after-the-fact reviews. However, balancing the burdens and benefits of risk alerts has always been an essential issue of CDSS (14-16). For csDDIs alerts in outpatients, choosing an appropriate drug combination cycle is important. There is a lack of research in this area.

This study aimed to investigate the prevalence and factors associated with potential DDIs, especially csDDIs, detected by Lexicomp®, Micromedex®, and DDInter in elderly outpatient prescriptions. Further, we aimed to assess the consistency of the 3 databases for rating DDIs and study the appropriate assessment cycle for potential csDDIs risk identification in CDSS for outpatients. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5463/rc) (17).

Methods

Study design and settings

This was a descriptive, observational, cross-sectional study conducted in PLA General Hospital in Beijing, which integrated medical service, education, and research. All prescriptions for elderly patients (≥65 years of age) were collected consecutively between January and March 2022. Patient-related information was retrieved from the hospital information system. The collection process ensured patient anonymity and data confidentiality. The study was conducted by the Declaration of Helsinki (as revised in 2013) and approved by PLA General Hospital Ethics Committee (No. S2022-497-01). Individual consent for this observational analysis was waived.

Participants

The target population was outpatients ≥65 years of age who had been prescribed at least 1 systemic drug (intravenous administration, gastrointestinal administration,

Table 1 Classification of DDIs in Lexicomp®, Micromedex®, and DDInter®

Database	Rating
Lexicomp	X (avoid combination)
	D (consider therapy modification)
	C (monitor Therapy)
	B (no Action Needed)
	A (no Known Interaction)
Micromedex	Contraindicated (the drugs are contraindicated for concurrent use)
	Major (interaction might be life-threatening and/or require medical intervention)
	Moderate (interaction might result in exacerbation of the patient's condition and/or requires an alternative therapy)
	Minor (interaction has limited clinical effects)
	Unknown (no known drug interactions)
DDInter	Major (interaction was highly clinically significant and the drug combinations should be strictly avoided)
	Moderate (interaction may result in exacerbation of the disease of the patient and/or change in therapy)
	Minor (interactions were minimally clinically significant and usually they do not require changes in therapy)
	Unknown (interaction description was unavailable or incomplete)

DDI, drug-drug interaction.

gastrointestinal administration, respiratory administration, rectal mucosal administration).

Data collection

The prescription inclusion criteria were as follows: Outpatient prescriptions for patients aged ≥65 years.

The prescription exclusion criteria were as follows: (I) prescriptions that do not include systemic medication; (II) prescriptions for traditional Chinese medicine (TCM) decoction preparations.

All systemic medications except Chinese patent medicines were involved in the DDI analysis. Chinese patent medicines were only counted in the patient's total number of drugs.

Different brands of medications with the same route of administration and the same generic name were considered 1 drug. Medications were classified according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system.

Medications for each patient were combined into pairs under different assessment cycles: (I) single prescription; (II) single day; (III) single period (prescriptions prescribed with intervals less than 7 days were counted as 1 period). Combinations were conducted after removing duplicate medications in a single assessment cycle.

This study had no interaction or direct contact with any patient. Age, gender, number of departments visited, number of medications, number of diagnoses, and the cost of medications for each patient were collected.

Evaluation of DDIs

All medication combinations were evaluated by 3 electronic databases: Lexicomp® Drug Interactions, Micromedex® Drug-Reax, and DDInter. Lexicomp® and Micromedex® were accessed through the hospital library. Drug combinations were classified according to the interaction risk of the different databases in *Table 1*. For compounded formulations, the corresponding drug was entered directly if it was available in the database, and the components included in the formulation were entered individually if it was not available in the database. All the drug combinations were entered independently by 2 trained pharmacists, with a third pharmacist participating in the case of any discrepancies in the results. The cut-off date for all database searches was 31 July 2022.

We defined the different rating DDIs into two classes. Potential DDIs including drug combinations: (I) X, D, C, B in Lexicomp®; (II) Contraindicated, Major, Moderate,

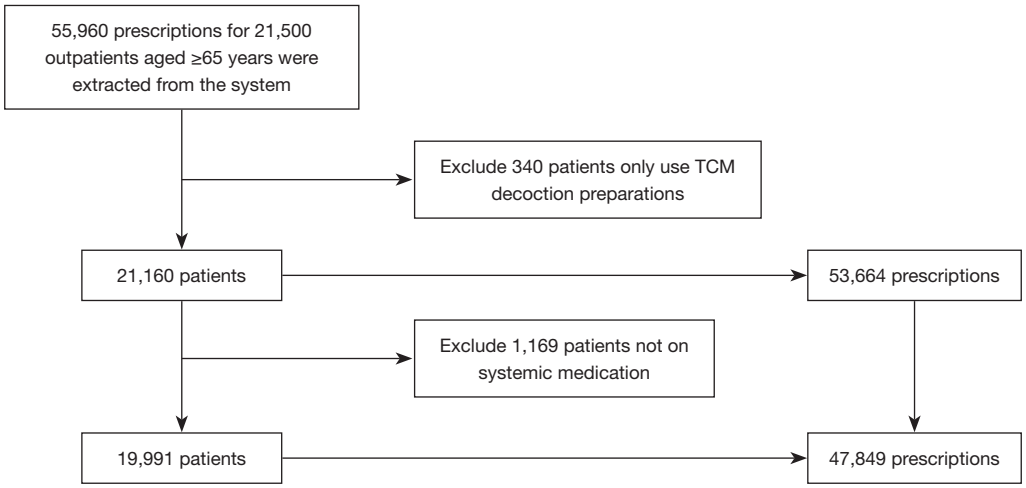

Figure 1 Patients inclusion and exclusion process. TCM, traditional Chinese medicine.

Minor in Micromedex®; (III) Major, Moderate, and Minor in DDInter. Potential csDDIs including drug combinations: (I) X and D in Lexicomp®; (II) Contraindicated and Major in Micromedex®; (III) Major in DDInter.

Statistical analysis

Data were analyzed with the statistical program SPSS 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables with normal distribution were presented as mean ± standard deviation (SD); non-normal variables were reported as the median and interquartile range (IQR).

The prevalence of different rating DDIs was expressed as a percentage. The prevalence of potential DDIs and csDDIs was expressed as the proportion of patients with at least 1 potential DDI or csDDI.

Univariate analysis was performed to assess the effect of covariates on the occurrence of csDDIs. To control for confounding variables, variables showing association in univariate analysis (P<0.2) were included in logistic regression analysis by forward procedures to identify variables that may be associated with potential csDDIs. Logistic regression analyses were presented with odds ratios (ORs) and 95% confidence intervals (95% CIs).

Database coverage of drugs refers to the proportion of all drugs involved in the interaction that could be retrieved in the database.

The consistencies were analyzed using weighted Cohen's kappa. Drug combinations that could be retrieved simultaneously from both databases were included in the analysis. Weighted kappa values of 0–0.2 indicated poor concordance; 0.21–0.40 indicated fair concordance; 0.41–0.60 indicated moderate concordance; 0.61–0.80 indicated strong concordance; and 0.81–1.0 indicated perfect concordance. The overlap was analyzed by jevenn (an interactive Venn diagram viewer) (18). A P value <0.05 was considered to indicate statistical significance.

Results

Participants

From January to March 2022, a total of 19,991 eligible patients were included. *Figure 1* describes the specific inclusion and exclusion process.

Characteristics of the study population

Of the 19,991 patients included, 45.8% were women. The median age of the patients was 71 years (IQR 67–69). Patients were prescribed 5–9 types of systemic drugs in 25.2% of cases, and 10 or more types in 7.9% of cases. There were 6,135 (30.7%) patients with more than 2 department visits, 3.2% with more than 5 visit days, and 34.5% with more than 2 visit periods. At different assessment cycles, 19,991 patients had different numbers of medications to be combined into pairs. When assessed with a single prescription, 12,252 patients had at least 1 drug combination; 13,439 patients when assessed within a single day, and 13,551 patients when assessed within a single period. *Table 2* shows the specific patient characteristics.

Table 2 Characteristics of the study population (N=19,991)

Characteristics	Data
Female, n (%)	9,149 (45.8)
Age, median [IQR]	71 [67–79]
65–69, n (%)	7,794 (39.0)
70–74, n (%)	4,514 (22.6)
75–79, n (%)	2,842 (14.2)
80–84, n (%)	2,314 (11.6)
85–89, n (%)	1,609 (8.0)
90–94, n (%)	823 (4.1)
≥95, n (%)	95 (0.5)
Types of departments patient visited, median [IQR]	1 [1–2]
1, n (%)	13,856 (69.3)
2–3, n (%)	4,860 (24.3)
4–6, n (%)	1,171 (5.9)
≥7, n (%)	104 (0.5)
Numbers of medications, median [IQR]	3 [2–5]
1–4, n (%)	13,375 (66.9)
5–9, n (%)	5,038 (25.2)
≥10, n (%)	1,578 (7.9)
Costs for medications (CNY), median [IQR]	835 [272–2,064]
Costs ≤500, n (%)	7,495 (37.5)
500< costs ≤1,000, n (%)	3,419 (17.1)
1,000< costs ≤2,000, n (%)	3,920 (19.6)
2,000< costs ≤5,000, n (%)	3,639 (18.2)
5,000< costs ≤10,000, n (%)	1,022 (5.1)
costs >10,000, n (%)	496 (2.5)
Numbers of prescriptions, median [IQR]	2 [1–3]
1–2, n (%)	14,055 (70.3)
3–5, n (%)	4,382 (21.9)
6–9, n (%)	1,154 (5.8)
≥10, n (%)	400 (2.0)
Numbers of visit days, median [IQR]	1 [1–2]
1, n (%)	12,394 (62.0)
2–4, n (%)	6,960 (34.8)
5–9, n (%)	615 (3.1)
≥10, n (%)	22 (0.1)
Numbers of consecutive visit periods, median [IQR]	1 [1–2]
1, n (%)	13,083 (65.4)
2–4, n (%)	6,661 (33.3)
≥5, n (%)	247 (1.2)

IQR, interquartile range.

Frequency and prevalence of potential DDIs and csDDIs

A total of 21,527 drug combinations were identified in patients. *Table 3* shows the number of different ratings of drug combinations. Lexicomp® detected 2,604 potential DDIs and 366 potential csDDIs. Micromedex® detected 1,411 potential DDIs and 740 potential csDDIs. DDInter detected 2,676 potential DDIs and 245 potential csDDIs.

Figure 2 demonstrates the frequency of potential DDIs and csDDIs during different assessment cycles. There are 214,344, and 128 csDDIs were identified during single prescription cycles by Lexicomp®, Micromedex®, and DDInter, respectively. When the assessment cycles extended to a single day, another 105, 298, and 95 csDDIs were detected, respectively. The frequency of csDDIs happened increased by 41.38% (1,798 to 2,542 in Lexicomp®), 53.86% (3,316 to 5,102 in Micromedex®), and 50.12% (812 to 1,219 in DDInter). When the assessment cycles expanded from a single day to a single period, the frequency of csDDIs increased by 5.9%, 6.0%, and 6.4%, respectively.

When DDIs were assessed with a single prescription, the prevalence of potential csDDIs was 2.93–10.59%. The prevalence increased by 2.28% (Lexicomp®), 3.37% (Micromedex®), and 1.41% (DDInter), when the assessment cycle was extended to 1 day. This further increased by 0.42%, 0.57%, and 0.22% when the assessment cycle was extended to 1 period. *Figure 3* demonstrates the prevalence of potential csDDIs and DDIs under different assessment cycles.

Characteristics of medications and departments patients visited

A total of 486 medications (excluding Chinese patent medicines) were prescribed for 19,991 patients, to a total of 67,177 times of patient use. The most used were ATC Class C (cardiovascular system class, 27.93%), Class A

Table 3 Numbers of drug combinations of different DDIs ratings (n=21,527)

Lexicomp		Micromedex		DDInter	
Rating	n	Rating	n	Rating	n
X	79	Contraindicated	4	Major	245
D	287	Major	736	Moderate	2,203
C	1,872	Moderate	645	Minor	228
B	366	Minor	26	Unknown	3,752
A	4	Unknown	0	None	5,158
None	14,835	None	13,497	–	9,941
–	4,084	–	6,619		

No interaction between the two drugs according to the feedback of the corre-sponding database. –, cannot be retrieved in the corresponding database. DDIs, drug-drug interactions.

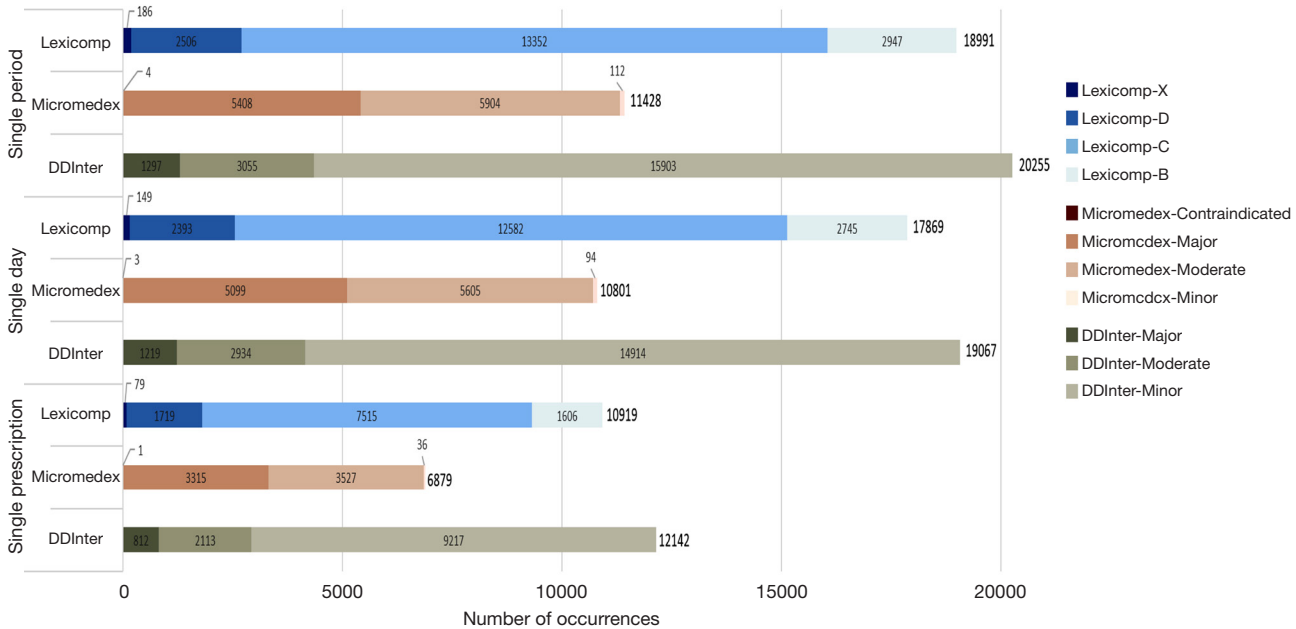

Figure 2 Frequency of potential DDIs and csDDIs under different assessment cycles. DDIs, drug-drug interactions; csDDIs, clinically significant drug-drug interactions.

(digestive and metabolic tract, 24.53%), Class B (blood and hematopoietic organs, 11.61%), and Class N (nervous system class, 11.50%). Among the 366 csDDIs evaluated by Lexicomp®, drugs used in diabetes (A10) participated in the most csDDIs (41.26%), followed by psycholeptics (N05, 18.85%) and anti-inflammatory and antirheumatic products (M01, 10.38%). Among the 740 csDDIs evaluated by Micromedex®, the most involved drug classes in the csDDIs were psychoanaleptics (N06, 30.68%), drugs used in diabetes (A10, 25.41%), and psycholeptics (N05, 17.16%). The top 3 drug classes involved in the 245 csDDIs evaluated by DDInter were psychoanaleptics (N06, 9.46%), immunosuppressants (L04, 7.7%), and agents acting on the renin-angiotensin system (C09, 6.62%). Table S1 shows the numbers of participating csDDIs and usage frequencies of each ATC category.

Studied outpatients visited a total of 40 types of departments. The department with the highest number of patient visits was Cardiology (60.40%), followed by Neurology (29.88%), and Gastroenterology (22.73%).

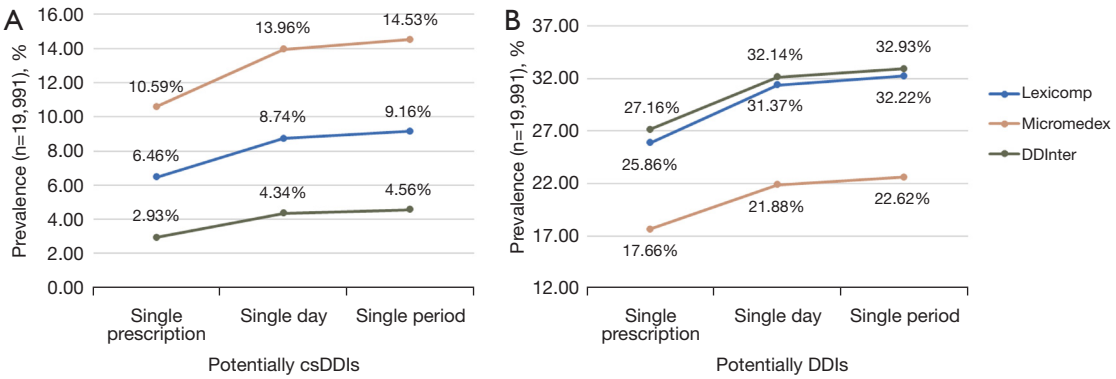

Figure 3 Prevalence of potential csDDIs and DDIs under different assessment cycles in three databases. DDIs, drug-drug interactions; csDDIs, clinically significant drug-drug interactions.

The factors of potential csDDIs

In the multifactorial analysis, regardless of the database used for DDIs assessment, polypharmacy and Neurology Department visits were risk factors for potential csDDIs. Visiting the Gastroenterology or TCM Department was a protective factor for the prevalence of potential csDDIs. Table S2 shows the results of univariate and multifactorial analyses of potential csDDIs when assessed within a single period.

For patients aged 70–74 years (OR 1.184, 95% CI: 1.075–1.304), ≥7 department visits (OR 10.357, 95% CI: 3.894–27.546), on multiple medications (5–9 medications, OR 9.267, 95% CI: 8.482–10.125; ≥10 medications, OR 44.859, 95% CI: 36.591–54.995), visiting the Cardiology (OR 1.536, 95% CI: 1.406–1.667), Neurology (OR 1.946, 95% CI: 1.754–2.160), Orthopedics (OR 1.396, 95% CI: 1.235–1.579), or Endocrinology (OR 2.634, 95% CI: 2.303–3.014) departments were at higher risk of having potential csDDIs under Lexicomp® criteria.

For those aged 70–74 years (OR 1.138, 95% CI: 1.012–1.279); with multiple medications (5–9 medications, OR 6.992, 95% CI: 6.261–7.808; ≥10 medications, OR 19.466, 95% CI: 16.328–23.208), visiting the Cardiology (OR 1.685, 95% CI: 1.521–1.866), Neurology (OR 2.305, 95% CI: 2.057–2.582), and Endocrinology departments (OR 2.415, 95% CI: 2.107–2.768) had a higher risk of having potential csDDIs under Micromedex® criteria.

For patients on multiple medications (5–9 medications, OR 4.479, 95% CI: 3.767–5.326; ≥10 medications, OR 12.64, 95% CI: 9.866–16.195), those seen in the Neurology department (OR 1.278, 95% CI: 1.079–1.513) were at higher risk of potential csDDIs under the DDInter criteria.

Consistency evaluation of the three databases

For 486 drugs, the coverage in Lexicomp® and Micromedex®, and DDInter databases was 427 (87.86%), 398 (81.89%), and 356 (73.25%), respectively. A total of 53 drugs were not included in any of the 3 databases.

Lexicomp® and Micromedex® retrieved 14,593 DDIs together, 11,489 for Lexicomp® and DDInter, and 11,432 for Micromedex® and DDInter. Weighted Kappa analysis of the 3 databases for the risk ratings of drug combinations showed moderate consistency for Lexicomp® and Micromedex® (weighted kappa =0.473) and fair consistency for both DDInter with the other 2 databases (0.364 with Lexicomp® and 0.303 with Micromedex®). *Figure 4* shows the overlap of csDDIs detected by the 3 databases. Sixty-six drug combinations were identified as csDDIs by all databases simultaneously.

Potential csDDIs detected by Lexicomp® and Micromedex® together

A total of 149 drug combinations were detected as csDDIs both in Lexicomp® and Micromedex®. These could be classified into 68 categories (Table S3). The most common (22/68) mechanism of drug interactions is that 1 drug enhances the pharmacological effects of another.

In a single prescription, only 83 combinations were detected. The most frequent combinations were aspirin and Ginkgo Biloba (113 times), aspirin and ticagrelor (72 times), and leflunomide and methotrexate (46 times).

There was an exponential increase in 18 categories (including 60 combinations) when the assessment cycles were extended to a single day. This was particularly noticeable for

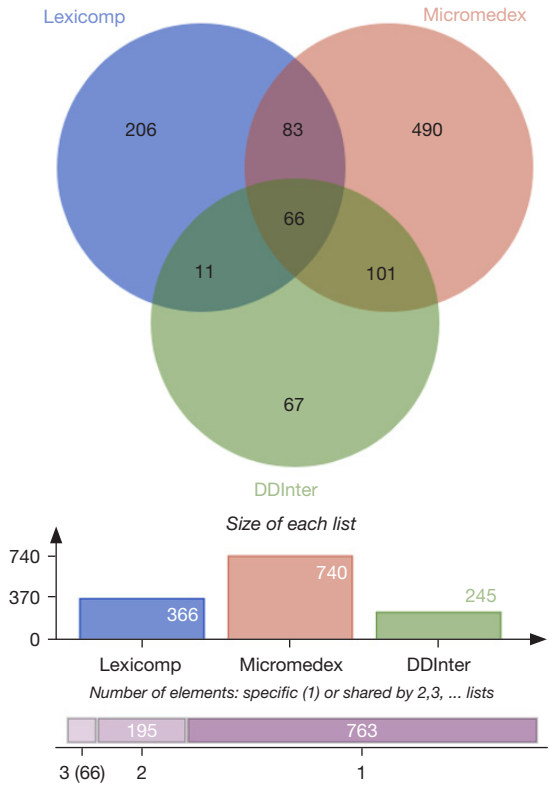

Figure 4 The overlap of csDDIs detected by the three databases. 66 drug combinations were identified as csDDIs by all databases simultaneously. DDIs, drug-drug interactions; csDDIs, clinically significant drug-drug interactions.

the combination of central nervous system (CNS) depressants and oxycodone, which increased from 2 to 107.

Only 2 combinations (atorvastatin and clarithromycin, citalopram and omeprazole) exponentially increased when the assessment period was extended from a single day to a single period.

Under any assessment cycle, the combination of aspirin and *Ginkgo biloba* was the most common combination. *Ginkgo biloba* may enhance the anticoagulant effect of aspirin and increase the bleeding risk. If the combination is used, it needs to be monitored for signs and symptoms of bleeding (especially intracranial bleeding).

Discussion

This study evaluated the consistencies of 2 classical commercial databases and 1 recently developed free database with 21,527 drug combinations in geriatric outpatients. Only the consistency between Lexicomp® and Micromedex® was moderate. The prevalence of potential csDDIs detected by the 3 databases ranged from 2.93% to 14.53% at different assessment cycles. Polypharmacy and Neurology Department visits were risk factors for potential csDDIs detected by all 3 databases. When the drug combination assessment cycle was expanded from single prescription to single visit day, the prevalence of csDDIs increased by 1.32–1.48 times.

DDIs in elderly outpatients showed widely heterogeneous results in previous studies. The prevalence of potential DDIs ranged from 20% to 100% (9). This heterogeneity was not only present in outpatient settings, but also in relevant studies in community and inpatient settings (19-21). These differences were partly due to study populations and regional differences; more importantly, the reasons included differences in the definition the DDIs (potential or clinically significant, especially for csDDIs) and the criteria evaluating DDIs (different databases, consensuses, and reference books). In this study, the prevalence can differ to about 10% (9.97% for potential csDDIs and 10.31% for potential DDIs) in the same population with different criteria. We defined the potential DDIs as drug combinations with interactions that can be retrieved from the database. Therefore, the types of "A" in Lexicomp® and "Unknown" in Micromedex® in DDInter® were not included. In some studies, csDDIs covered more combinations (22). Since DDIs in elderly patients are common, focusing on the DDIs with severe risks (such as life-threatening) that require avoiding combination or medical intervention is more practical. The consensuses related to csDDIs in elderly patients are also focused on this type of DDIs (23-27). The "C" risk rating in Lexicomp® requires monitoring the risk, and the DDIs rating "moderate" in Micromedex® indicates risk but is not life-threatening, so they were not included in potential csDDIs in our study.

The comparison research among different databases had already revealed that Micromedex® is the most commonly used software (28). Both Lexicomp® and Micromedex® showed the best performances (29,30). There were no studies of consistency analysis between Lexicomp® and Micromedex® in elderly patients. In other population research, the drug combinations evaluated for consistency were fewer and showed fair or moderate consistency of Lexicomp® and Micromedex® (31-35). In our study, a total of 21,527 drug combinations in elderly outpatient pharmaceuticals were examined. Some 17,758 drug combinations could be retrieved in at least 1 database. Lexicomp® and Micromedex® showed moderate

consistency with a weighted kappa of 0.473. DDInter® is a newly developed open-access drug interaction database (36) for which there has been no comparative study with other databases. Prescribing behavior of elderly patients is common due to the high prevalence of chronic diseases. In China, the accessibility of commercial databases for community pharmacists when reviewing medications for older patients is poor. It is necessary to find a reliable alternative tool. In this study, DDInter® showed fair consistency with the 2 classic commercial databases and had the lowest drug coverage. As in the other 2 databases, DDInter® describes risk rating, clinical effect, management advice, and references of each DDIs. However, there is no reliability rating in DDInter®. The investigator must retrieve drug components individually because DDInter® does not cover compounded formulations. Only a maximum of 5 drug components can be entered in 1 search, which reduced the efficiency of identification. However, at the same time, DDInter® has also demonstrated some advantages during the research process. It has a user-friendly interface; all drugs were ATC coded; each interaction was annotated with mechanisms, and alternative medications were provided based on the ATC code. We advise that DDInter® can be used as a simple alternative when commercial databases are not accessible to assess DDIs in elderly patients. Its recommendations can be used as a reference, but its reliability needs further strengthening.

Due to the variability in the risk ratings of DDIs, the factors associated with different databases are different. Polypharmacy was confirmed again in this study as a recognized risk factor for DDIs (19,34). For elderly outpatients, the risk increased by 4.479–9.267 times when using 5–9 medications and 12.64–44.859 times when using ≥10 medications. Notably, the risk of potential csDDIs did not increase with age. Multifactorial analysis under Lexicomp® and Micromedex® criteria showed that the risk of csDDIs was significant in patients aged 70–74 years in different age groups. However, the risk of potential csDDIs at age 80–89 years was lower in a multifactorial analysis of Micromedex®. This may be because physicians are more cautious in their prescribing practices for patients of advanced-age. The risk of potential csDDIs was only significantly elevated when the number of department visits was ≥7. Due to the disordered diagnosis in the outpatient prescription, it is hard to accurately evaluate the patient's disease distribution. Therefore, we counted the distribution of the departments visited by patients for substitution. Among the top 10 departments that patients visited, Neurology Department visits were a risk factor for potential csDDIs, regardless of the assessment criteria. This result was further confirmed by the fact that neurological drugs were ranked in the top 3 in the participation of csDDIs detected in all 3 databases.

In outpatient studies without direct contact with patients, researchers could not know all the information about the medications taken by patients. Therefore, an appropriate drug combination cycle is vital in evaluating DDIs and developing strategies for identifying outpatient DDIs in CDSS. Only evaluating the drug combinations within a single prescription will underestimate the DDIs. Extending the cycle unlimitedly will place more demands on the program, lead to oversensitivity, and increase the alert burden. Our study evaluated the changes in potential csDDIs in elderly outpatients with different drug combination cycles. Our findings demonstrated that the prevalence of potential csDDIs increased by 31.82–48.12%, the frequencies of potential csDDIs increased by 41.38–53.86%, the types of csDDIs detected were increased by 49–86% when the cycle was extended from a single prescription cycle to a single visit day. Meanwhile, when it was extended from a single day to a single visit period (with intervals less than 7 days), the prevalence increased by 4.08–5.07%, the frequencies increased by 5.9–6.4%, and the types increased by 9.87–15.26%. Therefore, identifying DDIs throughout the visit can avoid the omission of most csDDIs, especially for some csDDIs involved in drugs that need to be prescribed separately. For example, the interactions between oxycodone and CNS depressants were highly prevalent in our investigation. Since the increase in the prevalence and frequencies of potential csDDIs is not considerable and will increase the work burden of physicians (verifying the actual medication usage of patients), we propose only a targeted extension of the identification cycle for a small proportion of csDDIs with a very high risk involved in long-term medications for chronic diseases.

Although DDIs are predictable when clinical evidence and pharmacological effects are known (1), current CDSS for DDIs screening are often overly sensitive, with a high alert burden, and clinicians often override clinically significant and insignificant alerts (14). The factors of barriers in CDSS most often reported were related to (a lack of) usefulness and relevance of information (37). There have been few studies conducted related to the clinical outcomes of DDIs. Elderly patients are more susceptible to some of the risks for csDDIs identified in this study, such as

myopathy and QTc-prolonging. There are many outpatients with csDDIs that receive a combination of more than 2 CNS depressants. In Beers criteria, any combination of 3 or more CNS-active drugs needs to be avoided (24). Not only 2 drug interactions but also multiple drug interactions need to be considered (38). The lack of clinical relevance of the detected DDI should be addressed in upcoming studies, as this would provide more relevant information for prescribers in clinical practice. The strategy development for DDIs in CDSS needs a combination of more than 1 database, literature reviews, and advice from both expert physicians and pharmacists.

Strengths and limitations

The main strength of this study is the use of 2 well-established and reliable databases recognized from previous studies (Lexicomp® and Micromedex®) with a completely new database (DDInter) introduced to evaluate the same sample of larger (19,991 outpatients) elderly population (65 years and older) for comprehensive screening of DDIs (including 21,527 drug combinations) and assess changes of DDIs in outpatients with different combination cycles. It is the first consistent study of DDIs in elderly patients, the first use of the DDInter in clinical practice, and the first description of trends of DDIs in outpatients under different combination cycles. Some limitations of this study should also be highlighted. First, the evaluation was of potential DDIs and csDDIs, no clinical outcomes data were collected from patients to determine if the risk of interactions occurred. Second, this was a single-center study that only evaluated interactions between medications prescribed to elderly patients at the center, and did not collect complete medication data from patients, which would differ from the actual situation of patients. Third, some of the drug interactions were route- or dose-related; although we included systemic medications, we did not distinguish between IV or oral administration and we did not assess for the dose. Fourth, the use of Chinese patent medicines is widespread in elderly Chinese patients, and drug interactions with Chinese patent medicines were not evaluated in this study, and TCM decoction preparations were also excluded from the study.

Conclusions

More research on the risk of csDDIs is needed due to the inconsistency of DDIs ratings. In clinical pharmacotherapy practice, using multiple reference tools to evaluate DDIs and optimize the strategies is necessary. The use of neurologic drugs appears to predispose the elderly to csDDIs. Identifying medications prescribed for a full day allows for more accurate and comprehensive detection of csDDIs. DDIs risk strategies of CDSS should be multiple and individualized to be more effective in avoiding serious risks and optimizing pharmacotherapeutic outcomes.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5463/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5463/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by PLA General Hospital Ethics Committee (No. S2022-497-01). Individual consent for this observational analysis was waived.

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Supplementary

Table S1 The numbers of participating csDDIs and usage frequencies of each ATC category

ATC Classification (first level), Frequency, n (%)	second level	Frequency, n (%)	Numbers of participating csDDIs combinations, n (%)		
			Lexicomp (n=366)	Micromedex (n=740)	DDInter (n=245)
Alimentary Tract and Metabolism (A), 16478 (24.53)	A02	2685 (4.00)	37 (10.11)	37 (5)	9 (1.22)
	A03	1227 (1.83)	7 (1.91)	21 (2.84)	1 (0.14)
	A04	36 (0.05)	1 (0.27)	6 (0.81)	2 (0.27)
	A05	871 (1.30)	2 (0.55)	0	0
	A06	787 (1.17)	0	4 (0.54)	0
	A07	1136 (1.69)	10 (2.73)	5 (0.68)	1 (0.14)
	A09	610 (0.91)	0	0	0
	A10	4434 (6.60)	151 (41.26)	188 (25.41)	11 (1.49)
	A11	2762 (4.11)	9 (2.46)	4 (0.54)	0
	A12	1851 (2.76)	17 (4.64)	4 (0.54)	1 (0.14)
	A14	21 (0.03)	0	0	0
	A16	58 (0.09)	0	1 (0.14)	0
Blood and Blood Forming Organs (B), 7800 (11.61)	B01	4941 (7.36)	33 (9.02)	115 (15.54)	23 (3.11)
	B02	119 (0.18)	0	0	0
	B03	2409 (3.59)	11 (3.01)	4 (0.54)	2 (0.27)
	B05	331 (0.49)	8 (2.19)	3 (0.41)	16 (2.16)
Cardiovascular System (C), 18763 (27.93)	C01	2385 (3.55)	4 (1.09)	33 (4.46)	11 (1.49)
	C02	161 (0.24)	2 (0.55)	1 (0.14)	0
	C03	561 (0.84)	6 (1.64)	22 (2.97)	16 (2.16)
	C05	355 (0.53)	0	1 (0.14)	0
	C07	2557 (3.81)	3 (0.82)	22 (2.97)	14 (1.89)
	C08	3269 (4.87)	9 (2.46)	32 (4.32)	10 (1.35)
	C09	3231 (4.81)	25 (6.83)	66 (8.92)	49 (6.62)
	C10	6244 (9.29)	12 (3.28)	47 (6.35)	24 (3.24)
Dermatologicals (D), 13 (0.02)	D05	13 (0.02)	0	0	0
Genito Urinary System and Sex Hormones (G), 1915 (2.85)	G03	25 (0.04)	2 (0.55)	1 (0.14)	1 (0.14)
	G04	1890 (2.81)	5 (1.37)	23 (3.11)	2 (0.27)
Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins (H), 1070 (1.59)	H01	14 (0.02)	0	4 (0.54)	0
	H02	538 (0.8)	9 (2.46)	15 (2.03)	9 (1.22)
	H03	305 (0.45)	3 (0.82)	1 (0.14)	0
	H05	213 (0.32)	0	1 (0.14)	0
Antinfectives for Systemic Use (J), 2690 (4.00)	J01	1970 (2.93)	35 (9.56)	88 (11.89)	31 (4.19)
	J02	28 (0.04)	2 (0.55)	4 (0.54)	2 (0.27)
	J04	374 (0.56)	1 (0.27)	1 (0.14)	1 (0.14)
	J05	267 (0.40)	1 (0.27)	3 (0.41)	0
	J06	16 (0.02)	0	0	0
	J07	35 (0.05)	0	0	0
Antineoplastic and Immunomodulating Agents (L), 2626 (3.91)	L01	788 (1.17)	4 (1.09)	15 (2.03)	9 (1.22)
	L02	982 (1.46)	0	16 (2.16)	5 (0.68)
	L03	136 (0.20)	0	0	0
	L04	720 (1.07)	34 (9.29)	36 (4.86)	57 (7.7)
Musculo-Skeletal System (M), 3727 (5.55)	M01	2090 (3.11)	38 (10.38)	101 (13.65)	12 (1.62)
	M02	493 (0.73)	13 (3.55)	0	0
	M03	317 (0.47)	5 (1.37)	0	0
	M04	371 (0.55)	0	2 (0.27)	2 (0.27)
	M05	456 (0.68)	2 (0.55)	2 (0.27)	0
Nervous System (N), 7727 (11.50)	N01	18 (0.03)	0	1 (0.14)	0
	N02	391 (0.58)	33 (9.02)	41 (5.54)	28 (3.78)
	N03	802 (1.19)	29 (7.92)	52 (7.03)	18 (2.43)
	N04	625 (0.93)	11 (3.01)	10 (1.35)	2 (0.27)
	N05	2118 (3.15)	69 (18.85)	127 (17.16)	24 (3.24)
	N06	3061 (4.56)	26 (7.1)	227 (30.68)	70 (9.46)
	N07	712 (1.06)	13 (3.55)	1 (0.14)	0
Antiparasitic Products, Insecticides and Repellents (P), 263 (0.39)	P01	263 (0.39)	0	16 (2.16)	9 (1.22)
Respiratory System (R), 3453 (5.14)	R01	649 (0.97)	4 (1.09)	22 (2.97)	5 (0.68)
	R03	1147 (1.71)	18 (4.92)	32 (4.32)	3 (0.41)
	R05	853 (1.27)	1 (0.27)	2 (0.27)	0
	R06	803 (1.20)	18 (4.92)	10 (1.35)	4 (0.54)
	R07	1 (0)	0	0	0
Sensory Organs (S), 316 (0.47)	S01	316 (0.47)	7 (1.91)	9 (1.22)	5 (0.68)
Various (V), 336 (0.50)	V03	127 (0.19)	2 (0.55)	1 (0.14)	1 (0.14)
	V06	204 (0.30)	0	0	0
	V08	5 (0.01)	0	0	0

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Table S2 Univariate and multivariate analyses of potential csDDIs assessed within a single period

Variables	Detected by Lexicomp (n=1832)				Detected by Micromedex (n=2904)				Detected by DDInter (n=912)			
	n (%)	Univariate Analysis	Multivariate Analysis		n (%)	Univariate Analysis	Multivariate Analysis		n (%)	Univariate Analysis	Multivariate Analysis	
		Person Chi-Square	OR	95% CI		Person Chi-Square	OR	95% CI		Person Chi-Square	OR	95% CI
Gender												
Female	888 (9.7)	5.95*	1.0	–	1189 (13.0)	31.829**	1.0	–	407 (4.4)	0.499	1.0	–
Male	944 (8.7)		–	–	1715 (15.8)		–	–	505 (4.7)		–	–
Age												
65–69	656 (8.4)	9.194	1.0	–	986 (12.7)	40.661**	1.0	–	326 (4.2)	6.992	–	–
70–74	437 (9.7)		1.184**	1.075–1.304	687 (15.2)		1.138*	1.012–1.279	223 (4.9)		–	–
75–79	276 (9.7)		1.115	0.997–1.248	435 (15.3)		0.954	0.833–1.093	129 (4.5)		–	–
80–84	221 (9.6)		1.062	0.940–1.200	375 (16.2)		0.927	0.802–1.072	117 (5.1)		–	–
85–89	159 (9.9)		0.962	0.835–1.108	263 (16.4)		0.793*	0.671–0.937	78 (4.9)		–	–
90–94	75 (9.1)		0.953	0.788–1.153	144 (17.5)		0.869	0.699–1.080	37 (4.5)		–	–
≥95	8 (8.4)		0.924	0.546–1.563	14 (14.7)		0.56	0.298–1.052	2 (2.1)			
No. of departments												
1	852 (6.1)	3**	1.0	–	1381 (10.0)	1036.25**	1.0	–	467 (3.4)	309.652**	1.0	–
2–3	626 (12.9)		0.974	0.871–1.091	1028 (21.2)		0.672**	0.594–0.759	272 (5.6)		0.75*	0.622–0.904
4–6	310 (26.5)		1.242	0.957–1.611	437 (37.3)		0.53**	0.419–0.669	151 (12.9)		0.99	0.725–1.352
≥7	44 (42.3)		10.357**	3.894–27.546	58 (55.8)		0.959	0.584–1.575	22 (21.2)		1.887*	1.031–3.456
No. of medications												
1–4	502 (3.8)	2**	1.0	–	727 (5.4)	3046.981**	1.0	–	274 (2.0)	808.638**	1.0	–
5–9	804 (16.0)		9.267**	8.482–10.125	1427 (28.3)		6.992**	6.261–7.808	378 (7.5)		4.479**	3.767–5.326
≥10	526 (33.3)		44.859**	36.591–54.995	750 (47.5)		19.466**	16.328–23.208	260 (16.5)		12.64**	9.866–16.195
Department patient visited												
Cardiology	763 (11.5)	64.747**	1.536**	1.406–1.677	1617 (24.4)	773.506**	1.685**	1.521–1.866	433 (6.5)	87.706**	–	–
Neurology	415 (12.6)	56.935**	1.946**	1.754–2.160	837 (25.5)	380.207**	2.305**	2.057–2.582	235 (7.2)	60.722**	1.278*	1.079–1.513
Gastroenterology	283 (11.3)	16.073**	0.353**	0.308–0.404	384 (15.4)	1.645	0.569**	0.489–0.661	150 (6.0)	13.648**	0.777*	0.630–0.959
Orthopedics	451 (19.5)	333.668**	1.396**	1.235–1.579	448 (19.3)	48.664**	0.865*	0.749–0.998	114 (4.9)	0.763	–	–
Pneumology	313 (13.7)	63.846**	0.605**	0.530–0.690	505 (22.1)	119.444**	–	–	143 (6.3)	17.094**	0.719*	0.580–0.890
Urinary	170 (8.4)	1.656	0.526**	0.456–0.606	303 (14.9)	0.312	–	–	98 (4.8)	0.379	–	–
Endocrinology	462 (27.7)	753.518**	2.634**	2.303–3.014	523 (31.4)	417.045**	2.415**	2.107–2.768	76 (4.6)	0	–	–
TCM	204 (15.2)	62.799**	0.412**	0.348–0.489	290 (21.6)	57.909**	0.671**	0.563–0.799	85 (6.3)	10.325*	0.568**	0.434–0.745
Nephrology	107 (10.3)	1.639	–	–	150 (14.4)	0.012	–	–	50 (4.8)	0.147	–	–
Oncology	65 (6.9)	5.903*	0.522**	0.422–0.647	75 (8.0)	33.808**	–	–	35 (3.7)	1.56	–	–

*, P<0.05; **, P<0.001.

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Table S3 The potential csDDIs detected by both Lexicomp and Micromedex and their frequencies

Object drug and class	Interacting drug and class	Lexicomp Rating	Micromedex Rating	Frequency under different assessment cycles, n		
				Single prescription	Single day	Single period
Alpha-/Beta-Agonists	Serotonin/Norepinephrine Reuptake Inhibitors	D	Major	0	2	2
Alpha1-Agonists	Monoamine Oxidase Inhibitors	X	Major	2	2	2
Alpha1-Blockers	Alpha1-Blockers	X	Major	2	4	4
Amlodipine	Simvastatin	D	Major	12	15	15
Angiotensin-Converting Enzyme Inhibitors	Angiotensin II Receptor Blockers	D	Major	10	15	18
Anti-Parkinson Agents (Dopamine Agonist)	Antipsychotic Agents (Second Generation [Atypical])	D	Major	2	8	10
Aspirin	Dabigatran Etexilate	D	Major	9	12	12
Aspirin	Nonsteroidal Anti-Inflammatory Agents (COX-2 Selective)	D	Major	2	11	15
Aspirin	Ticagrelor	D	Major	72	83	83
Atorvastatin	Clarithromycin	D	Major	0	1	3
Atorvastatin	Cyclosporine	X	Major	2	5	6
Beta-Blockers	Rivastigmine	X	Major	2	2	2
Carbamazepine	Quetiapine	D	Major	0	1	1
Cardiac Glycosides	Amiodarone	D	Major	1	1	1
Cilostazol	Omeprazole	D	Major	0	1	1
Citalopram	Escitalopram	X	Major	2	2	3
Citalopram	Omeprazole	D	Major	0	1	2
Clopidogrel	CYP2C19 Inhibitors (Strong)	D	Major	0	1	1
Clopidogrel	Omeprazole/Esomeprazole	X	Major	6	17	25
Clopidogrel	Repaglinide	D	Major	6	15	15
CNS Depressants	Opioid Agonists	D	Major	17	20	22
CNS Depressants	Oxycodone	D	Major	2	107	117
CNS Depressants	Zolpidem	D	Major	53	102	112
Cyclosporine (Systemic)	Antifungal Agents (Azole Derivatives, Systemic)	D	Major	0	1	1
CYP3A4 Inducers (Moderate)	Clarithromycin	D	Major	1	1	1
Dabigatran Etexilate	Nonsteroidal Anti-Inflammatory Agents (Nonselective)	D	Major	0	3	3
Diltiazem	Simvastatin	D	Major	1	2	2
Domperidone	CYP3A4 Inhibitors (Moderate)	X	Major	1	1	1
Domperidone	Ondansetron	D	Major	1	1	1
Domperidone	QT-prolonging Agents (Moderate Risk)	D	Major	1	1	1
Felodipine	CYP3A4 Inducers (Strong)	D	Major	1	1	1
Felodipine	CYP3A4 Inhibitors (Strong)	D	Major	0	1	1
Gefitinib	Inhibitors of the Proton Pump (PPIs and PCABs)	D	Major	0	0	1
Hormonal Contraceptives	CYP3A4 Inducers (Weak)	D	Major	0	1	1
Insulins	Dipeptidyl Peptidase-IV Inhibitors	D	Major	24	31	31
Insulins	Liraglutide	D	Major	18	21	21
Insulins	Pioglitazone	D	Major	1	3	3
Ivabradine	CYP3A4 Inhibitors (Moderate)	X	Major	3	5	6
Lamotrigine	Valproate Products	D	Major	3	3	3
Lev amlodipine	Simvastatin	D	Major	21	24	25
Levofloxacin	Amiodarone	X	Major	0	1	1
Loop Diuretics	Nonsteroidal Anti-Inflammatory Agents	D	Major	1	3	3
Methotrexate	Inhibitors of the Proton Pump (PPIs and PCABs)	D	Major	1	3	4
Methotrexate	Leflunomide	D	Major	46	46	46
Methotrexate	Nonsteroidal Anti-Inflammatory Agents	D	Major	12	13	13
Metoclopramide	Promethazine	X	Major	1	4	4
Nonsteroidal Anti-Inflammatory Agents	Nonsteroidal Anti-Inflammatory Agents	X	Major	3	8	12
QT-prolonging Miscellaneous Agents (Moderate Risk)	QT-prolonging Strong CYP3A4 Inhibitors (Moderate Risk)	X	Major	0	2	2
Rivaroxaban	Antiplatelet Agents (P2Y12 Inhibitors)	D	Major	3	3	3
Rivaroxaban	Aspirin	D	Major	2	4	5
Rivaroxaban	Nonsteroidal Anti-Inflammatory Agents (Nonselective)	D	Major	0	2	2
Rosuvastatin	Brand Name	D	Major	1	3	3
Salicylates	Ginkgo Biloba	D	Major	113	161	169
Salicylates	Methotrexate	D	Major	1	2	2
Salicylates	Nonsteroidal Anti-Inflammatory Agents (Nonselective)	D	Major	9	54	63
Selective Serotonin Reuptake Inhibitors	Nonsteroidal Anti-Inflammatory Agents (Nonselective)	D	Major	0	8	11
Selegiline	Selective Serotonin Reuptake Inhibitors	X	Contraindicated	0	1	1
Serotonergic Non-Opioid CNS Depressants	Selegiline	X	Contraindicated	1	1	1
Silodosin	CYP3A4 Inhibitors (Strong)	X	Contraindicated	0	0	1
Sulfamethoxazole and Trimethoprim	Methotrexate	D	Major	1	1	1
Sulfonylureas	Alpha-Glucosidase Inhibitors	D	Major	24	24	24
Sulfonylureas	Dipeptidyl Peptidase-IV Inhibitors	D	Major	47	51	51
Sulfonylureas	Thiazolidinediones	D	Major	3	3	3
Tenofovir Products	Nonsteroidal Anti-Inflammatory Agents	D	Major	0	1	1
Tetracyclines	Magnesium Salts	D	Major	0	1	1
Tiotropium	Anticholinergic Agents	X	Major	9	12	15
Tolvaptan	CYP3A4 Inhibitors (Moderate)	D	Major	1	1	1
Vitamin K Antagonists	Ginkgo Biloba	D	Major	1	1	1

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