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Original Article

Exploring Potential Drug-Drug Interactions: A Cross-Sectional Study of 1 Million e-Prescriptions Across Medical Specialties in Shiraz, Iran (2021-2024)

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What's Known

- Drug-drug interactions can cause serious adverse effects and are a common prescribing error.
- Studies in various countries, including Iran, have documented the prevalence of potential drug-drug interactions, but recent, large-scale data across multiple medical specialties in Iran is lacking.

What's New

- This study of over one million prescriptions reveals that 38.77 percent contain a potential drug-drug interaction, with 12.98 percent of all prescriptions involving high-risk combinations.
- This research identified dexamethasone, ketorolac, and quetiapine as the drugs most frequently involved in potential interactions and presented the most common interactions, distinguished by specialty.

Abstract

Background: Drug-drug interactions (DDIs) are among the most important medical errors that can lead to adverse effects, increased toxicity, or reduced treatment efficacy. The frequency and severity of DDIs vary across specialties. However, studies covering multiple specialties in Iran are few and not up-to-date. This study aims to fill this gap by offering a large-scale, multi-specialty analysis of DDIs in Iran using real-world e-prescription data.

Methods: This study analyzed pharmacological DDIs in 1,049,769 e-prescription records from Shiraz, Iran, spanning from November 2021 to February 2024. We used Lexicomp® DDI checker software and Python programming language to identify the most prevalent DDIs overall, the top contributing drug specialties for each of those DDIs, the specialties with the highest rates of potential DDIs, and the most prevalent DDI within each specialty.

Results: The analysis revealed that 38.77% of prescriptions contained at least one C, D, or X DDI. Dexamethasone, ketorolac, quetiapine, and aspirin were the drugs most commonly involved. The most frequent DDIs occurred between aprepitant and dexamethasone, ketorolac, and naproxen, aprepitant and doxorubicin, prednisolone, and tacrolimus, and diclofenac sodium and ketorolac. The medical specialties with the highest incidence of D or X level DDIs were rheumatology, endocrinology, orthopedics, oncology, internal medicine, emergency services, and psychiatry. The average counts of D or X DDIs per prescription were 0.53, 0.41, 0.40, 0.40, 0.26, 0.24, and 0.23, respectively.

Conclusion: This study underscores the need for provider vigilance and proactive measures, such as training and e-prescription alerts, to ensure patient safety.

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Keywords ● Drug interactions ● Electronic prescribing ● Prevalence ● Cross-sectional studies ● Iran

Introduction

The treatment of complex diseases often requires the simultaneous use of multiple drugs, but this method may cause interactions between the drugs that can lead to side effects and even failure of the treatment. Potential drug-drug interactions (DDIs) are one of the common errors in prescribing medications, and studies show

that a significant number of these DDIs is severe or moderate in therapeutic terms.[1]

DDI is a distinct form of adverse drug event that arises when one medication alters the action of another, potentially leading to heightened toxicity or diminished therapeutic benefit. DDIs are especially prevalent in hospital environments, where patients frequently receive multiple medications simultaneously.[2] Potential DDIs are a common cause of adverse drug events, significantly contributing to patient morbidity and rising healthcare costs. They can reduce medication effectiveness, increase toxicity, and undermine patient adherence to prescribed treatment plans.[3, 4] It is estimated that this results in increased hospital stays, which incurs an approximate annual cost of US$ 1 billion to the healthcare system.[5]

Potential DDIs are avoidable,[4] and tools such as Lexicomp®, Medscape®, and Drugs.com exist for checking DDIs. In this regard, studies indicate that Lexicomp®, which is a subsidiary of UpToDate®, has higher accuracy.[6, 7]

Extensive research on DDIs has been conducted both internationally and domestically. International studies—from countries such as Greece, Denmark, Sweden, Finland, Nepal, and others—have highlighted the common occurrence of DDIs in clinical settings.[8-15] Similarly, domestic investigations in Shiraz have demonstrated the clinical significance of DDIs among diverse patient populations.[5, 16, 17] However, a gap remains in the literature: only one study, published in 2011, has explored the frequency of DDIs across various medical specialties and among general practitioners in Iran, with limited studies worldwide focusing on medical specialties and the most frequent DDIs in each specialty.[15, 18] This gap underscores the need for further research to fully understand the distribution and impact of DDIs in different clinical contexts, particularly in Iran.

To the best of our knowledge, no recent studies have examined the frequency of potential pharmacological DDIs across various medical specialties, including general practitioners in Iran, since the 2011 study. This study aims to address this gap by identifying the most prevalent DDIs overall, the top contributing drug specialties for each DDI, the specialties with the highest rates of potential DDIs, and the most prevalent DDI within each specialty, using a dataset of 1 million electronic prescriptions (e-prescriptions).

Materials and Methods

A total of 1,049,769 anonymous e-prescription records were collected from treatment centers in Shiraz, comprising 479,770 from Salamat Insurance and 569,999 from Tamin Insurance, over the period from November 2021 to February 2024. All e-prescriptions issued during this timeframe were included in the study; no random sampling was performed. The data were provided by the Information Technology Center at Shiraz University of Medical Sciences in a fully pre-anonymized format. In other words, all direct personal identifiers (such as the names of patients and prescribing doctors) and indirect identifiers (such as date of birth, residential area, and unique prescription codes) had been removed from the dataset before our access. Consequently, the research team never had access to identifiable patient information. Due to the retrospective design and the use of pre-anonymized data, obtaining individual consent from each patient was not feasible. The study protocol was reviewed and approved by the Research Ethics Committee of the School of Medicine, Shiraz University of Medical Sciences, which confirmed that the project was conducted in accordance with ethical principles and the national norms and standards for medical research in Iran (reference number: IR.SUMS.MED.REC.1403.642). The prescriptions were analyzed using Lexicomp® DDI checker software (version 2023; Wolters Kluwer, the Netherlands) for potential DDI assessment. This tool was selected because previous studies have demonstrated that it provides a higher level of accuracy than other similar tools.[6, 7] Since levels A and B DDIs are not clinically significant, they are not included in this report. According to guideline recommendations, these categories represent interactions that either lack meaningful clinical effects or have such a low likelihood of causing harm that no intervention is necessary.[3, 19, 20] The classification of DDIs (A, B, C, D, and X) and their definitions are presented in table 1.[3]

All data processing and descriptive statistical analysis were performed using Python (version 3.10.9, Python Software Foundation, United States), Pandas library (version 1.5.3, NumFOCUS/PyData, United States),[21] and NumPy (version 1.23.5, NumPy Developers/NumFOCUS, USA).[22] Our Python script uses Iran's generic drug codes and then searches for them in the Lexicomp® software. Due to the complexity of mapping local Iranian drug codes to an international database and the large volume of data, a custom computational pipeline was developed. The key stages of this pipeline are detailed below.

Table 1: Classification of DDIs and their definitions

Classification	Interaction	Definition
A	No intervention specified	Evidence shows no interaction affecting pharmacodynamics or pharmacokinetics.
B	No action needed	Evidence shows drug interactions occurring simultaneously without clinical concern.
C	Monitor therapy	Evidence shows that drug interactions can result in clinical symptoms, but the benefits of using these drugs together outweigh the potential risks. Close monitoring is required to identify any adverse effects, and dosage modifications for one or both drugs may be necessary.
D	Consider therapy modification	Evidence shows potential clinical interactions. Each patient should be assessed individually to see if the benefits outweigh the risks. Steps may be needed to reduce toxicity, including intensive monitoring, dosage changes, or alternative treatments.
X	Preventing the interaction	Evidence shows interactions with clinical side effects. The risks generally outweigh the benefits.

Initial Data Cleaning and Standardization

Raw prescription data, containing drug details and physician specialties, were loaded into Pandas DataFrames. This involved:

a) Creating a unique list of Iranian generic drug codes from the entire dataset to serve as a master reference.

b) Standardizing drug names by systematically replacing local variations and abbreviations with consistent terminology. This process was guided by a manually curated replacement list (e.g., standardizing "valproate Sodium" to "valproic Acid"). This list was manually created to handle exceptions and drug names that failed to be identified by the primary search algorithm described below. This pre-processing step was crucial for improving the accuracy of subsequent database lookups.

Drug Name Parsing and Ingredient Extraction

A significant challenge was that Iranian drug names often contain multiple pieces of information (e.g., active ingredient, salt form, dosage) within a single string. A rule-based parsing code was built to deconstruct these names:

a) Regular expressions were used to identify and separate the core ingredient from information in parentheses (e.g., extracting "as hydrochloride" from "dapoxetine [as hydrochloride]").

b) The parenthetical text was further classified into categories such as salt forms (e.g., "as metformin hydrochloride"), formulation numbers (e.g., "cold adult 4-2"), or protein sources (e.g., "recombinant").

c) For combination drugs, identified by a "/" separator, the script splits the string into a list of individual active ingredients (e.g., parsing "losartan potassium/hydrochlorothiazide" into "losartan potassium" and "hydrochlorothiazide").

d) The route of administration (e.g., topical, systemic, ophthalmic) was also programmatically extracted from the full drug name string to aid in disambiguation during the mapping stage.

Mapping Iranian Drugs to the Lexicomp® Database

The core of our analysis involved mapping the extracted Iranian drug ingredients to their corresponding generic drug entries in the Lexicomp® database. This was a multi-step, hierarchical search process:

a) Direct search: The script first attempted to find an exact, case-insensitive match for the extracted ingredient in the Lexicomp® generic table.

b) Wildcard search: If no exact match was found, a LIKE structured query language (SQL) query was used to find ingredients starting with the same name.

c) Brand name search: If the generic search failed, the script then searched the Lexicomp® brand table, as some local generic names correspond to international brand names.

d) Salt-stripping search: For drugs with identified salt forms, if the full name (e.g., "metformin hydrochloride") failed to yield a match, the script would search again using only the core ingredient ("metformin").

e) Route disambiguation: In cases where a search returned multiple Lexicomp® entries for the same drug (e.g., systemic vs. topical formulations), the previously extracted route of administration was used to select the correct database entry.

For each successfully mapped Iranian drug, its corresponding Lexicomp® category_id(s) were retrieved. These IDs are essential for querying the interactions table.

DDI Analysis

For each prescription containing two or more successfully mapped drugs, the following analysis was performed:

a) The script compiled a list of all Lexicomp® category_ids for all drugs in the prescription.

b) Using Python's combinations function, it generated every possible two-drug pair within the prescription.

c) For each pair, a query was executed against the Lexicomp® monograph table to find any documented interactions, checking for the drugs in both the object_id and precipitant_id columns.

d) It is possible for a single drug pair to have multiple documented interactions with varying risk levels in the Lexicomp® database. When multiple interactions were found for a single pair, the one with the highest risk level (where X=5, D=4, C=3, B=2, A=1) was selected as the primary interaction.

Table 2: Total count and top most frequently prescribed drugs across different physician specialties

Specialty	Prescription count	Prescriptions with polypharmacy	Drugs count	Injectable drug	Top most frequent drugs	Top most frequent injectable drugs
All physicians	1049769 (100.0%)	431604 (41.1%)	3895071 (100.0%)	131100 (3.4%)	1) Sodium chloride (Parenteral):114745 (2.9%) 2) Pantoprazole (As sodium sesquihydrate) (Oral):85329 (2.2%) 3) Dexamethasone (as disodium phosphate) (Parenteral):77978 (2.0%) 4) Acetaminophen (Oral):65292 (1.7%) 5) Famotidine (Oral):60583 (1.6%)	1) Acetaminophen (Intravenous):50524 (38.5%) 2) Granisetron (Intravenous):31600 (24.1%) 3) Dextrose / Sodium chloride (Intravenous):18087 (13.8%) 4) Carboplatin (Intravenous):6057 (4.6%) 5) Docetaxel (Intravenous):5637 (4.3%)
General practitioner	176746 (16.8%)	113410 (64.2%)	827631 (21.2%)	50914 (6.2%)	1) Sodium chloride (Parenteral):76767 (9.3%) 2) Ketorolac trometamol (Parenteral):46029 (5.6%) 3) Acetaminophen (Intravenous):45038 (5.4%) 4) Azithromycin (Oral):40099 (4.8%) 5) Ondansetron (Parenteral):33488 (4.0%)	1) Acetaminophen (Intravenous):45038 (88.5%) 2) Dextrose / Sodium Chloride (Intravenous):4570 (9.0%) 3) Dextrose (Intravenous):571 (1.1%) 4) Trifluoperazine (Intramuscular):249 (0.5%) 5) Furosemide (Intravenous):179 (0.4%)
Oncology	109940 (10.5%)	53499 (48.7%)	498664 (12.8%)	58761 (11.8%)	1) Dexamethasone (as disodium phosphate) (Parenteral):34819 (7.0%) 2) Granisetron (Intravenous):27601 (5.5%) 3) Sodium chloride (Parenteral):24211 (4.9%) 4) Aprepitant (Oral):19453 (3.9%) 5) Filgrastim (Parenteral):18095 (3.6%)	1) Granisetron (Intravenous):27601 (47.0%) 2) Dextrose / Sodium Chloride (Intravenous):10002 (17.0%) 3) Carboplatin (Intravenous):4917 (8.4%) 4) Docetaxel (Intravenous):4874 (8.3%) 5) Dextrose (Intravenous):3666 (6.2%)
Neurologists	104968 (10.0%)	37997 (36.2%)	361923 (9.3%)	1674 (0.5%)	1) Gabapentin (Oral):21498 (5.9%) 2) Meloxicam (Oral):11876 (3.3%) 3) Famotidine (Oral):11716 (3.2%) 4) Propranolol hydrochloride (Oral):11432 (3.2%) 5) Pantoprazole (as sodium sesquihydrate) (Oral):10285 (2.8%)	1) Ibuprofen (Intravenous):1099 (65.7%) 2) Immune Globulin (Intravenous):342 (20.4%) 3) Acetaminophen (Intravenous):140 (8.4%) 4) Dextrose / Sodium Chloride (Intravenous):50 (3.0%) 5) Dextrose (Intravenous):9 (0.5%)

(| sign separates interacting drugs, and / sign is used for compounded drugs). *The summaries were gathered from Lexicomp®. If the specialty was unknown, it was categorized as 'Others.' Prescriptions with four or more, which four drugs are considered as polypharmacy.

e) The results, including the drug pair, risk level (C, D, or X), summary, and management advice, were appended to a final results DataFrame. As mentioned, DDI levels A and B were excluded from the final analysis.

Descriptive Report

Using the obtained DDI results, we employed the Pandas library to compute the descriptive statistics for this study. The data were grouped by medical specialty and by specific DDI pairs to determine overall frequencies, prevalence rates, and the most common DDIs (along with the specialties that most frequently prescribed them). The top DDIs within each specialty were identified and presented in a separate table. Data visualization was conducted using the Seaborn (version 0.13.2, Michael Waskom/PyData, United States) and Matplotlib (version 3.9.1, Matplotlib Development Team/NumFOCUS, United States) Python packages.[23, 24]

Results

The details of how many prescriptions each specialty has, the number of prescriptions with four or more drugs (considered polypharmacy), the portion of injectable drugs, and the most frequently prescribed drugs in each specialty are shown in table 2 (total count and top most frequently prescribed drugs across different physician specialties). The results showed that 136,242 prescriptions (12.98%) included at least one D or X DDI, and 407,031 prescriptions (38.77%) had at least one C, D, or X DDI from all 1,049,769 prescription records. Figure 1 (counts and percentages of C, D, and X DDIs across all prescriptions) presents a bar chart showing the counts of A, B, C, D, and X level DDIs across all prescriptions, as well as the percentage of each relative to the total number of DDIs. Figure 2 (top 20 drugs most frequently involved in DDIs) illustrates the most frequently occurring drugs in all DDIs. While figure 3 (average D or X DDIs per prescription by specialty) presents the D or X DDI count per prescription by specialty. The most common potential DDIs, along with the specialties of the five types of physicians most frequently responsible for these errors, are listed in table 3 (the top 50 most common X or D interactions along with the top 5 physician specialties). These DDIs are sorted by their frequency of occurrence in prescriptions, and due to the large number of DDIs, only the top 50 most frequent are included. Additionally, the table lists the top 5 most frequent D or X DDIs within each specialty. Among the identified DDIs, certain drugs and drug pairs appeared frequently across prescriptions, revealing notable patterns in prescribing practices.

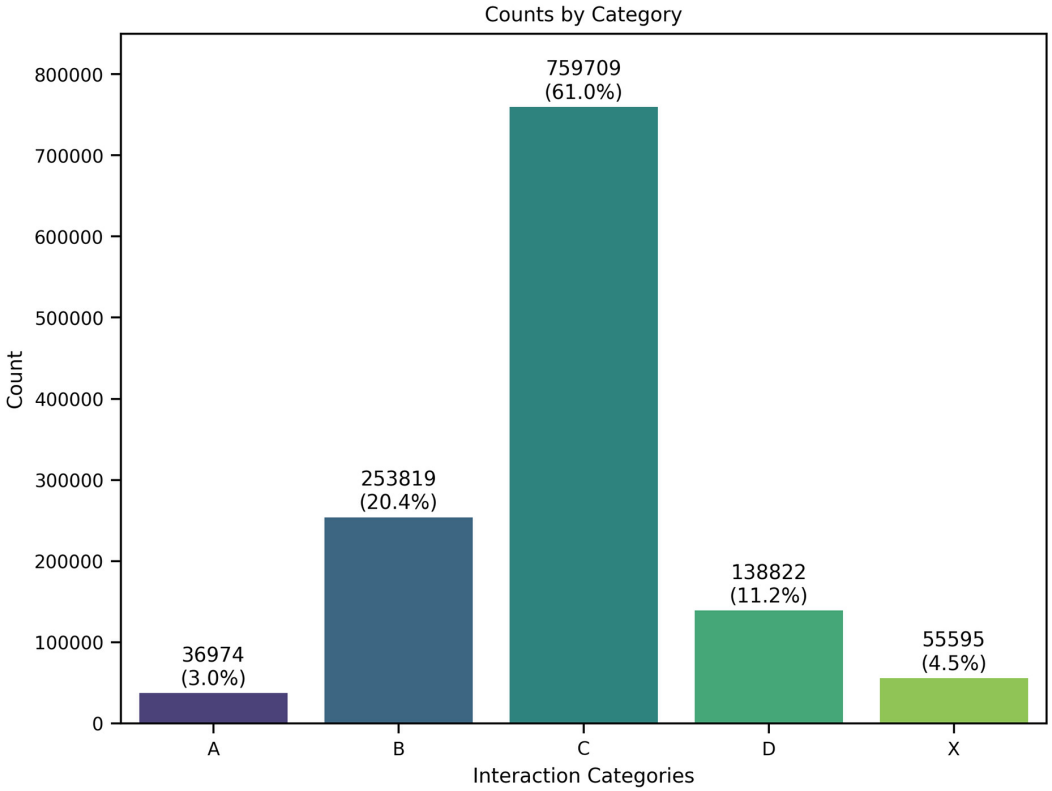

Figure 1: The bar chart displays the absolute counts of C, D, and X-type DDIs, as well as their percentages relative to the total number of DDIs identified across all e-prescriptions.

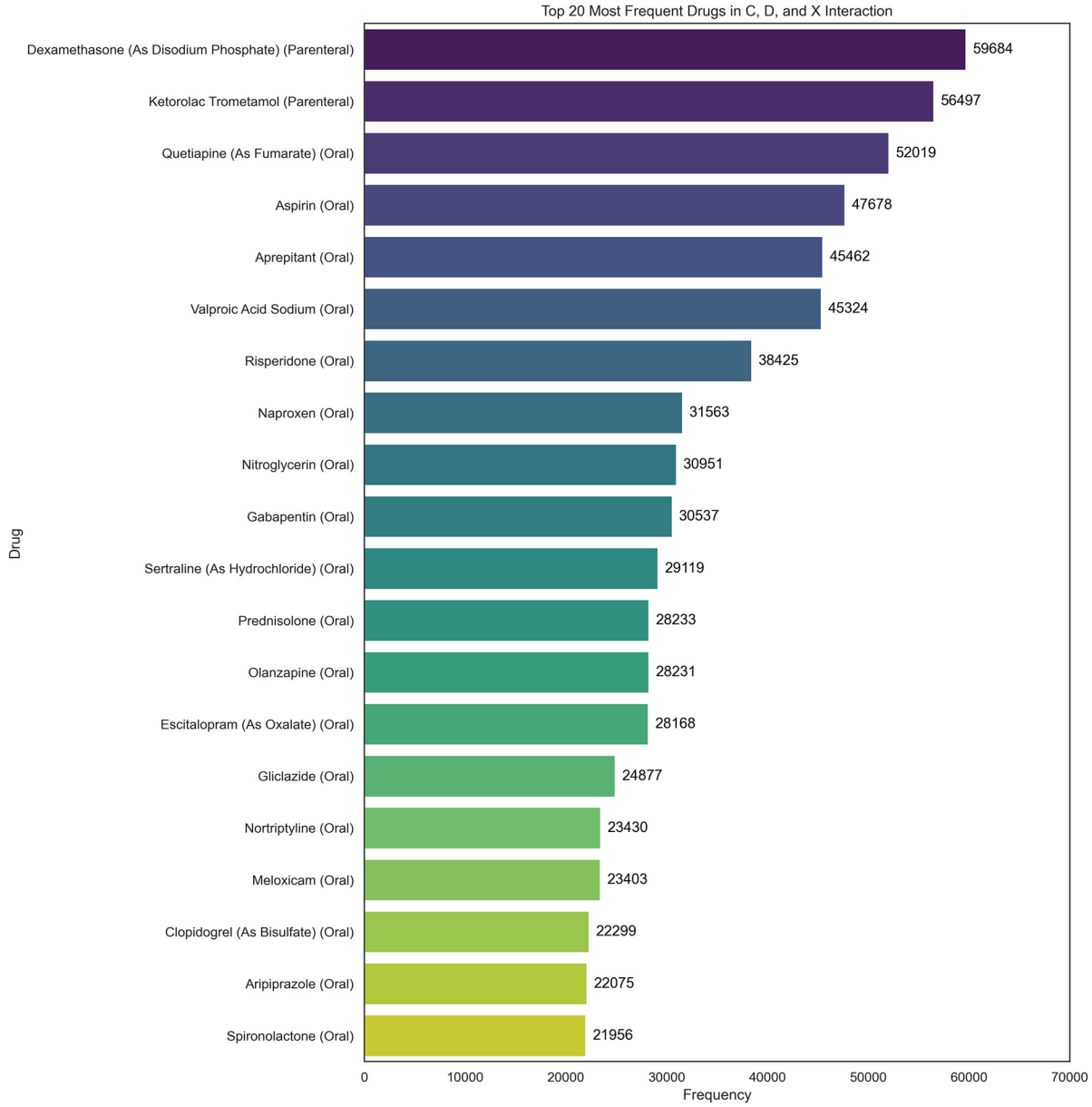

Figure 2: This figure shows the ranking of the top 20 drugs most frequently involved in potential DDIs of C, D, or X severity. The horizontal bar chart illustrates the total number of interactions attributed to each specific drug across all analyzed prescriptions. Drug names are listed on the Y-axis, and the corresponding total interaction count is shown on the X-axis.

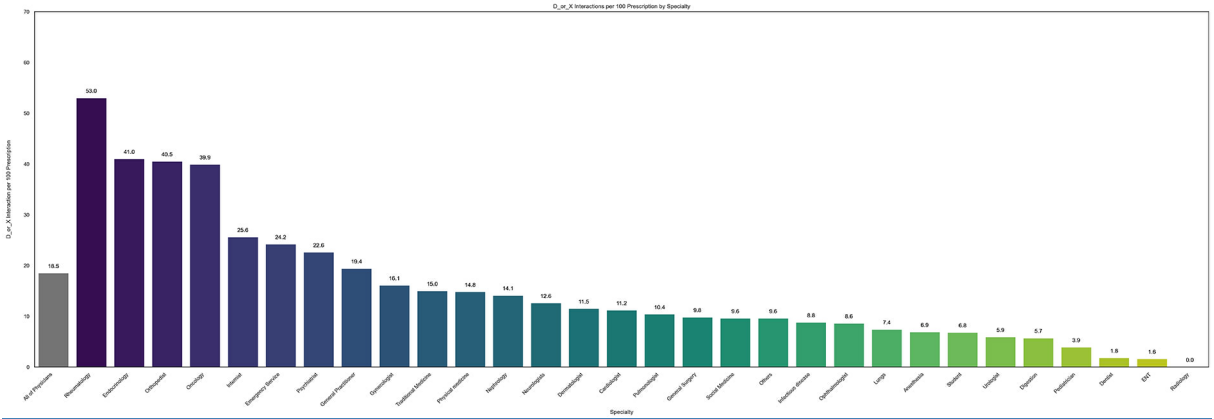

Figure 3: The chart displays the average number of D or X interactions per prescription for each specialty, allowing comparison of prescribing patterns derived from the collected e-prescription records. Specialties are ordered from the highest to the lowest rate of potential DDIs.

Table 3: The top 50 most common X or D interactions, along with the top 5 physician specialties

Interaction	Occurrence count (%)	Risk	Severity	Reliability	Summary	Top 5 specialties
Aprepitant (Oral) |Dexamethasone (as disodium phosphate) (Parenteral)	21952 (11.3%)	D	Moderate	Good	Aprepitant may increase the serum concentration of Corticosteroids (Systemic).	Oncology: 18635 (84.9%) Internist: 3060 (13.9%) Gynecologist: 249 (1.1%) Infectious disease: 4 (0.0%) Psychiatrist: 1 (0.0%)
Ketorolac trometamol (Parenteral) | Naproxen (Oral)	10907 (5.6%)	X	Moderate	Fair	Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of ketorolac (Systemic).	General Practitioner: 10198 (95.6%) Orthopedist: 208 (1.9%) Internist: 100 (0.9%) Oncology: 99 (0.9%) Neurologists: 65 (0.6%)
Aprepitant (Oral) | Doxorubicin hydrochloride (Parenteral)	6956 (3.6%)	X	Moderate	Good	CYP3A4 Inhibitors (Moderate) may increase the serum concentration of DOXOrubicin (Conventional).	Oncology: 5956 (85.6%) Internist: 979 (14.1%) Pediatrician: 16 (0.2%) Infectious disease: 3 (0.0%) Neurologists: 2 (0.0%)
Carboplatin (Intravenous) | Paclitaxel (Parenteral)	4279 (2.2%)	D	Major	Fair	Platinum Derivatives may enhance the myelosuppressive effect of Taxane Derivatives. Administer Taxane derivative before Platinum derivative when given as sequential infusions to limit toxicity.	Oncology: 3720 (86.9%) Gynecologist: 327 (7.6%) Internist: 231 (5.4%) Infectious disease: 1 (0.0%)

(| sign separates interacting drugs and / sign is used for compounded drugs). *The summaries were gathered from Lexicomp®. If the specialty was unknown, it was categorized as 'Others.'

The most common DDIs involved dexamethasone, ketorolac, quetiapine, aspirin, and valproic acid. In addition, the most common DDIs were between aprepitant and dexamethasone, ketorolac and naproxen, aprepitant and doxorubicin, prednisolone and tacrolimus, and diclofenac sodium and ketorolac. The majority (33 out of 50, or 66%) were classified as having moderate severity, while 17 interactions (34%) were categorized as major severity according to Lexicomp®. Regarding the reliability of the evidence supporting these interactions, 36 (72%) were rated as fair, 9 (18%) as good, 4 (8%) as excellent, and 1 (2%) as poor. In table 4 (each specialty's total prescriptions, D or X interaction count, and the top 5 most frequent D or X interactions for each specialty), each specialty of doctor expertise is displayed along with the total number of prescriptions and the count of X or D DDIs. The highest incidence of D- or X-level DDIs per prescription was observed in rheumatology, endocrinology, orthopedics, oncology, internal medicine, emergency medicine, and psychiatry. The average number of D- or X-level DDIs per prescription in these specialties was 0.53, 0.41, 0.40, 0.40, 0.26, 0.24, and 0.23, respectively. The complete version and a detailed list of all specialties presented in Supplementary Tables 1-3.

Discussion

In this study, we analyzed over one million e-prescription records to assess the prevalence and nature of potential DDIs across various medical specialties. Our finding regarding the percentage of prescriptions containing at least one high-risk (D or X) DDI is comparable to international reports, although the prevalence rates vary considerably. For example, studies in Nepal[8] (in a hospital setting with handwritten prescriptions) found rates as high as 78%, while electronically screened outpatient prescriptions in Egypt[9] and Greece[10] reported rates between 17% and 18%. In Finland's assisted living facilities, the prevalence of severe interactions was 5.9%.[13] Overall, differences in prevalence across studies likely stem from variations in prescribing practices, patient populations, and methodological approaches.[10] Additionally, it is important to consider that prescribing practices in Iran exhibit notable differences from global standards, which may influence the prevalence and interpretation of DDIs in this context. For instance, studies have shown that while the availability and affordability of essential medicines in Iran are generally good, the country often falls short of international benchmarks regarding rational medicine use and prescribing behaviors.[25]

Table 4: Each specialty's total prescriptions, D or X interaction count, and the top 5 most frequent D or X interactions for each specialty

Speciality	Total prescriptions	C	D	X	D_or_X	D_or_X per 100 prescriptions	Top 5 most frequent D_or_X interactions	Risk	Severity	Reliability	Interaction summaries
All physicians	1049769 (100.0%)	759709 (100.0%)	138822 (100.0%)	55595 (100.0%)	194417 (100.0%)	18.5	1) Aprepitant (Oral) | Dexamethasone (as disodium phosphate) (Parenteral) 2) Ketorolac trometamol (Parenteral) | Naproxen (Oral) 3) Aprepitant (Oral) | Doxorubicin hydrochloride (Parenteral) 4) Carboplatin (Intravenous) | Paclitaxel (Parenteral) 5) Gliclazide (Oral) | Sitagliptin (as phosphate) / Metformin hydrochloride (Oral)	1) D 2) X 3) X 4) D 5) D	1) Moderate 2) Moderate 3) Moderate 4) Major 5) Moderate	1) Good 2) Fair 3) Good 4) Fair 5) Good	1) Aprepitant may increase the serum concentration of corticosteroids (Systemic). 2) Nonsteroidal Anti-inflammatory agents may enhance the adverse/toxic effect of ketorolac (Systemic). 3) CYP3A4 inhibitors (Moderate) may increase the serum concentration of DOXOrubicin (Conventional). 4) Platinum derivatives may enhance the myelosuppressive effect of taxane derivatives. Administer taxane derivative before platinum derivative when given as sequential infusions to limit toxicity. 5) Dipeptidyl peptidase-IV inhibitors may enhance the hypoglycemic effect of Sulfonylureas.
Rheumatology	17888 (1.7%)	15542 (2.0%)	9277 (6.7%)	199 (0.4%)	9476 (4.9%)	53	1) Leflunomide (Oral) | Prednisolone (Oral):2659 2) Leflunomide (Oral) | Methotrexate Sodium (Oral):2255 3) Methotrexate Sodium (Oral) | Pantoprazole (As Sodium Sesquihydrate) (Oral):828 4) Leflunomide (Oral) | Methotrexate Sodium (Parenteral):691 5) Methotrexate Sodium (Oral) | Naproxen (Oral):483	1) D 2) D 3) D 4) D 5) D	1) Moderate 2) Moderate 3) Moderate 4) Moderate 5) Major	1) Fair 2) Excellent 3) Fair: Existing data/ reports are inconsistent 4) Excellent 5) Good	1) Corticosteroids (Systemic) may enhance the immunosuppressive effect of leflunomide. 2) Methotrexate may enhance the adverse/toxic effects of Leflunomide. Specifically, the risks of hepatoxicity and hematologic toxicity may be increased. 3) Inhibitors of the Proton Pump (PPIs and PCABs) may increase the serum concentration of methotrexate. 4) Methotrexate may enhance the adverse/toxic effect of leflunomide. Specifically, the risks of hepatoxicity and hematologic toxicity may be increased. 5) Nonsteroidal anti-inflammatory agents may increase the serum concentration of methotrexate.

Endocrinology	36849 (3.5%)	26226 (3.5%)	14870 (10.7%)	221 (0.4%)	15091 (7.8%)	41	1) Gliclazide (Oral) | Pioglitazone (Oral):2113 2) Gliclazide (Oral) | Sitagliptin (As Phosphate) / Metformin Hydrochloride (Oral):2028 3) Empagliflozin / Linagliptin (Oral) | Gliclazide (Oral):1593 4) Empagliflozin / Metformin hydrochloride (Oral) | Gliclazide (Oral):1166 5) Acarbose (Oral) | Gliclazide (Oral):908	1) D 2) D 3) D 4) D 5) D	1) Moderate 2) Moderate 3) Moderate 4) Moderate 5) Moderate	1) Fair 2) Good 3) Fair 4) Fair 5) Fair	1) Thiazolidinediones may enhance the hypoglycemic effect of sulfonylureas. 2) Dipeptidyl Peptidase-IV Inhibitors may enhance the hypoglycemic effect of Sulfonylureas. 3) Sodium-glucose cotransporter 2 (SGLT2) inhibitors may enhance the hypoglycemic effect of Sulfonylureas. 4) Sodium-glucose cotransporter 2 (SGLT2) inhibitors may enhance the hypoglycemic effect of Sulfonylureas. 5) Alpha-Glucosidase Inhibitors may enhance the hypoglycemic effect of Sulfonylureas.
Orthopedy					13039 (6.7%)	40.5	1) Meloxicam (Oral) | Piroxicam (Topical):2773 2) Ketorolac Trometamol (Parenteral) | Meloxicam (Oral):1697 3) Diclofenac sodium (Parenteral) | Meloxicam (Oral):1372 4) Diclofenac sodium (Parenteral) | Ketorolac trometamol (Parenteral):994 5) Diclofenac sodium (Rectal) | Enoxaparin sodium (Parenteral):594	1) D 2) X 3) X 4) X 5) D	1) Moderate 2) Major 3) Major 4) Major 5) Moderate	1) Fair 2) Fair 3) Fair 4) Fair 5) Fair	1) Nonsteroidal anti-inflammatory agents (Topical) may enhance the adverse/toxic effect of nonsteroidal anti-inflammatory agents. Specifically, the risk of gastrointestinal (GI) toxicity is increased. 2) Nonsteroidal anti-inflammatory agents may enhance the adverse/toxic effect of other nonsteroidal anti-inflammatory agents. Specifically, the risk for gastrointestinal toxicity is increased. 3) Nonsteroidal anti-inflammatory agents may enhance the adverse/toxic effect of other nonsteroidal anti-inflammatory agents. Specifically, the risk for gastrointestinal toxicity is increased. 4) Nonsteroidal anti-inflammatory agents may enhance the adverse/toxic effect of other nonsteroidal Anti-inflammatory agents. Specifically, the risk for gastrointestinal toxicity is increased. 5) Nonsteroidal anti-inflammatory agents may enhance the anticoagulant effect of enoxaparin.

(| sign separates interacting drugs and / sign is used for compounded drugs). * The summaries were gathered from Lexicomp®. If the specialty was unknown, it was categorized as 'Others'. The table was sorted by 'D or X per Prescription' column.

Factors contributing to these differences include higher average numbers of medicines per prescription, a tendency among younger physicians to prescribe more medications, and widespread irrational prescribing practices when compared to international norms.[26]

The majority of the 50 most common DDIs identified in our study were classified as having moderate severity. These DDIs could have serious consequences for patients, such as increased toxicity, reduced efficacy, or adverse reactions.[3] For example, dexamethasone is metabolized primarily via the cytochrome P450 3A4 (CYP3A4) pathway. It can act as both an inducer and a substrate of CYP3A4, causing changes in the metabolism of co-administered drugs. DDIs may result in either increased toxicity (through inhibited clearance) or decreased efficacy (through enhanced clearance), particularly with drugs also metabolized by CYP3A4 or those affecting P-glycoprotein. High-dose dexamethasone, especially as seen in recent COVID-19 protocols, amplifies this.[27] Additionally, the use of multiple nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of serious gastrointestinal complications, and this risk escalates with higher doses and the concurrent use of multiple agents.[28] These top-most frequent DDIs differ from those identified in other international contexts. For example, studies from Greece have highlighted frequent amlodipine–simvastatin DDIs, while research from Nepal has reported common pairs such as aspirin–clopidogrel.[8, 10] These variations suggest that critical DDI risks are not universal but are influenced by local clinical practices, patient populations, and prescribing patterns. Therefore, effective patient safety interventions should be tailored based on using local data, as relying solely on imported guidelines may overlook the most prevalent risks within our healthcare system.

Our analysis highlights that the highest rates of potentially significant DDIs were concentrated in specialties such as rheumatology, endocrinology, and orthopedics. This pattern is not surprising, as it reflects the inherent complexity of managing chronic diseases that often necessitate polypharmacy with high-risk medications. For instance, the frequent DDIs observed in rheumatology arise from the standard practice of combining multiple immunosuppressive agents to control the disease. Similarly, in endocrinology, achieving glycemic targets in diabetes often requires using several classes of antidiabetic drugs simultaneously, which may increase the risk of hypoglycemia. The prevalence of interactions in orthopedics, primarily involving the concurrent use of multiple NSAIDs, underscores the challenges of managing severe pain and inflammation effectively.[29-32] It should be noted that our study lacks data on the order of drug administration and patient indications. As a result, most identified DDIs are pharmacological rather than clinical. For instance, some DDIs categorized as C, D, or X in the Lexicomp® DDI software can often be managed by considering the clinical indication and adjusting the timing of drug administration, rather than being inherently dangerous (e.g., administering ketorolac alongside other NSAIDs, according to Lexicomp®). Additionally, in certain cases, the simultaneous administration of interacting drugs is necessary, particularly in chemotherapy, autoimmune diseases, and diabetes management. Table 5 highlights some of these considerations.[32, 33] Although the Lexicomp® software provides recommendations for managing these DDIs, our study's lack of administration order and patient indication data presents a limitation. This may have led to an overestimation of DDI rates in some specialties, such as oncology. It is noteworthy that this may be due to an imbalanced dataset, in which certain specialties—such as radiology—report a low incidence of D or X DDIs per prescription, in this case, a value of 0. This result is likely due to the lower number of prescriptions from these specialties in our dataset.

When comparing our findings with those of Ahmadizar and colleagues (2011) and a study from Bangladesh, notable variations emerge in the distribution of major DDIs across specialties. Ahmadizar and colleagues found that cardiologists, internists, and psychiatrists most frequently prescribed medications with severe DDIs, while the Bangladesh study reported cardiologists, gynecologists, and general practitioners as the specialties with the highest incidence of such DDIs.[15, 18] These discrepancies may result from various factors, including changes in prescribing practices, increased drug safety awareness, and updates in clinical guidelines over the past 15 years. Additionally, variations in sample populations, data collection methodologies, and healthcare infrastructure may have contributed to these differences. Further research is needed to determine whether these changes reflect improvements in prescribing safety or evolving risk patterns among specialties.

To mitigate the risks associated with DDIs, various strategies could have been investigated. Several interventions have been explored to reduce DDIs, notably the implementation

Table 5: Therapeutic drug combinations in oncology and autoimmune care: indications, interactions, and monitoring

Drug – Drug interaction	Clinical indications	Concurrent usage: recommendations and example indications
Aprepitant (Oral) | Dexamethasone (as disodium phosphate) (Parenteral)	✓ Chemotherapy-induced nausea and vomiting (CINV) The CINV management guidelines suggest using aprepitant in conjunction with a serotonin antagonist and dexamethasone to prevent nausea and vomiting caused by highly and moderately emetogenic chemotherapy. The recommended combination is aprepitant, palonosetron, and dexamethasone.	Administer 125 mg of aprepitant 1 hour before chemotherapy on day 1, then 80 mg daily for the next two days (days 2 and 3), alongside a 5-HT3 antagonist antiemetic on day 1 and dexamethasone from days 1 to 4
Carboplatin (Intravenous) | Paclitaxel (Parenteral) (PC or carbotaxol regimen)	✓ Adjuvant treatment of high-risk, stage I, epithelial ovarian cancer ✓ Treatment of advanced ovarian cancer ✓ Treatment of primary peritoneal cancer ✓ Treatment of fallopian tube cancer ✓ Treatment of recurrent or advanced endometrial cancer (stage III or IV) ✓ Treatment of advanced/recurrent non-small cell (NSC) cancer of the cervix ✓ Treatment of carcinoma of unknown primary site	To minimize toxicity, paclitaxel should be administered prior to carboplatin when they are given as sequential infusions. For paclitaxel: Dose: 200 mg/m² IV Dilute in 250 mL of normal saline (NS) and infuse over one hour, using specialized tubing. For carboplatin: AUCΔ: 6 mg/mL per min IV Dilute in 250 mL of NS and infuse over 30 min.
Leflunomide (Oral) | Prednisolone (Oral)	✓ Myasthenia gravis (MG) ✓ Rheumatoid arthritis ✓ Progressive IgA nephropathy	Adjust the schedule for routine monitoring of platelet count, white blood cell count, and hemoglobin or hematocrit to once a month, rather than every 6 to 8 weeks, for patients on systemic corticosteroids. ➢ This recommendation applies to individuals receiving systemic corticosteroids at doses greater than 2 mg/Kg or 20 mg/day of prednisone (for those over 10 kg) for a duration exceeding 2 weeks.
Leflunomide (Oral) | Methotrexate sodium (Oral)	✓ Rheumatoid arthritis	When leflunomide is used alongside methotrexate, start leflunomide at 20 mg once daily without a loading dose. Monitor for signs of methotrexate-related liver toxicity (ALT, AST, and serum albumin) at least every 2 to 4 weeks during the first 3 months of treatment, then every 8 to 12 weeks between months 3 and 6, and every 12 weeks for patients on this combination for more than 6 months. Additionally, check platelet count, white blood cell count, and hemoglobin or hematocrit monthly. If bone marrow toxicity is detected, discontinue leflunomide and initiate an accelerated drug elimination process.
Docetaxel (Intravenous) | Oxaliplatin (Parenteral)	✓ Advanced gastric cancer ✓ Gastroesophageal adenocarcinomas ✓ Advanced pancreatic ductal adenocarcinoma ✓ Locally advanced and metastatic non-small-cell lung cancer (NSCLC)	To reduce toxicity, administer the taxane derivative before the platinum derivative when given as sequential infusions. The DOC regimen, which combines docetaxel with oxaliplatin and capecitabine, involves administering docetaxel at 60 mg/m², diluted in 500 mL of NS, as a one-hour infusion. This is followed by oxaliplatin at 100 mg/m², diluted in 500 ml of 5% dextrose, given as a two-hour infusion on day 1. Capecitabine is taken continuously at 500 mg/m² orally twice daily. The treatment cycles are repeated every three weeks.
Polypharmacy with oral antidiabetic agents*	✓ Severe, uncontrolled diabetes	

of clinical decision support systems (CDSS) integrated within electronic health records to alert providers of high-priority DDIs based on criteria such as severity, probability, and clinical implications.[34] Furthermore, the integration of artificial intelligence (AI) has enhanced CDSS capabilities by analyzing complex drug interactions, identifying potential adverse drug reactions, and suggesting optimal drug combinations and regimens, thereby improving physician efficiency and patient safety.[35]

This study contributes to the existing literature through several of its features. By analyzing a large dataset of over 1 million e-prescriptions, our findings provide a recent and detailed view of DDI prevalence in this specific region. Using data from 2021-2024 offers an updated perspective on prescribing patterns. Furthermore, the

analysis at the specialty level allows for a more granular understanding of where DDIs are most common, which may be useful for guiding future educational efforts.

There are, however, some limitations to consider in our study. One limitation of our study is that we used Lexicomp®, which does not include many herbal drugs commonly used in Persian prescriptions. Additionally, our dataset lacks information on the order of drug administration and patient indications, meaning we cannot determine whether the drugs in a single prescription were intended to be used simultaneously or on different days. This limitation may have contributed to an overestimation of DDI rates in certain specialties, such as oncology, where concurrent use of interacting drugs is sometimes necessary. Future studies should aim to incorporate data on administration timing and patient-specific indications to provide a more accurate assessment of clinical DDIs. Additionally, the number of prescriptions varies between specialties in our dataset. Although we used the frequency of D or X DDIs per prescription to minimize the impact of this discrepancy, it may still influence the results. This approach may not fully capture some common DDIs within specialties that have few prescriptions in our dataset, such as radiology. We utilized a substantial dataset (over 1 million prescription records), necessitating the use of the Python programming language for data management. This approach allowed conducting a more extensive analysis, helping us identify the most frequent prescriptions within each specialty. Although we meticulously debugged and tested the Python program, the possibility of rare, unintended errors or omissions remains a limitation. Future research could benefit from integrating machine learning techniques to enhance data validation and improve the detection of clinically significant DDIs. Another limitation is that our data comes exclusively from therapy centers in Shiraz, all of which are supervised by Shiraz University of Medical Sciences. This may limit the generalizability of our findings to other regions or healthcare settings. Expanding future studies to include data from multiple geographic locations and different healthcare systems could help provide a more comprehensive understanding of DDIs across various medical practices.

Conclusion

In our study, we found that 38.77% of prescriptions in Shiraz, Iran, involve at least one potential DDI classified as C, D, or X, which is significant. The drugs most frequently involved in these higher-risk interaction categories were dexamethasone, ketorolac, quetiapine, aspirin, and valproic acid. Additionally, we have compiled a list of the five most common DDIs for each medical specialty. This study suggests that DDIs are a problem that requires more attention and intervention from healthcare providers, policymakers, and researchers. Addressing DDIs through enhanced prescription monitoring, targeted interventions, additional specialty-specific training programs, the integration of alerts into e-prescription systems, and other potential solutions—such as employing AI—could offer a promising approach to this challenge and potentially improve patient safety.

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During the preparation of this work, the authors used the GPT-4o large language model to improve the grammar and readability of the text. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Authors' Contribution

P.P: Conceptualization, methodology, formal analysis, investigation, visualization, writing original draft. M.H. Investigation, formal analysis, writing, review, and editing. Ne. A: Investigation, formal analysis, writing review, and editing. Mo.S: Conceptualization, formal analysis, Writing, review, and editing. Na. A: Conceptualization, methodology, formal analysis, Writing, review, and editing. Me.S: Supervision, conceptualization, methodology, writing, review, and editing. All authors have read and approved the final manuscript and agree to be 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.

Declaration of AI

During the preparation of this work, the authors used the GPT-4o large language model to improve the grammar and readability of the text. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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