



INVESTIGATING THE FACTORS AFFECTING DRUG-DRUG INTERACTIONS

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ABSTRACT

A drug-drug interaction (DDI) is a change in the effect of a drug when administered with another drug or group of drugs. Drug interactions are common and cause increased hospital admission rates, treatment failure, avoidable medical complications, and even deaths. A literature survey is conducted to find factors affecting drug-drug interactions in cohorts that are more likely to be affected by drug-drug interactions. The study found age related factors and multiple drug usage to be reasons for drug-drug interactions, agreeing with previous studies. In addition large cohort studies of general nature were found to be necessary to identify potential DDIs. DDIs being a major concern even in pediatric wards, the methodology of their identification is significantly important to improve pharmacovigilance. The drug interaction checking applications will become more effective if the interactions are correctly identified.

KEYWORDS: ADVERSE DRUG EFFECTS, DRUG-DRUG INTERACTIONS, DRUG SAFETY, EPIDEMIOLOGY, POLYPHARMACY, PHARMACOVIGILANCE.



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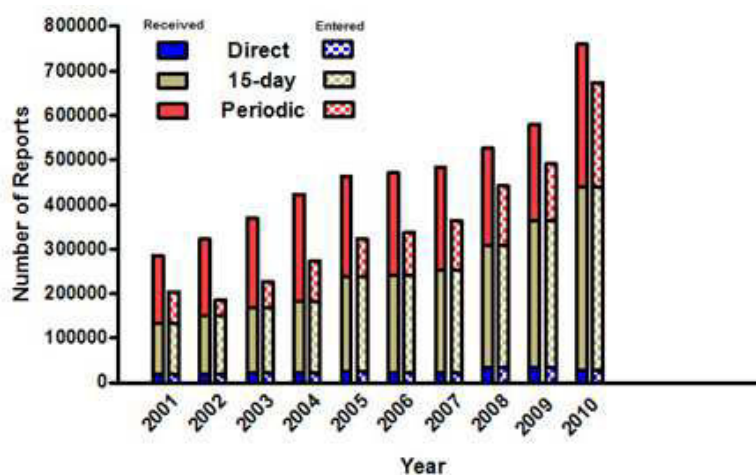
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INTRODUCTION

The incidence of potential drug-drug interactions is close to 40% in patients taking 5 drugs and 80% in patients taking 7 or more medications¹. Drug adverse reactions cause up to 5% hospital admissions, 28% emergency room visits, and 5% hospital deaths^{2,3,4}. The occurrence of drug interactions is reported to be a permanent cause of risk even in pediatric hospitals⁵. Due to the number of drugs needed to treat comorbidities in the elderly and the strong correlation between increasing age and the number of drugs prescribed, the potential for drug-drug interactions is found to be higher in the elderly in relation to other demographics^{6,7,8,9}. According to Leidholm, elderly patients experience DDIs at a higher frequency than their younger counterparts¹⁰. Additionally, almost 5% of hospitalizations in the elderly are due to DDIs¹¹. This is of immense importance because senior citizens aged 65 and above account for approximately 15% of the Western population and receive almost one-third of all drug prescriptions¹². Clearly, improvement in drug safety will be invaluable in terms of morbidity and mortality. In addition, advancement in drug

safety through the identification of DDIs will have positive economic consequences^{13,39}. Almost 10% of general hospital admissions are caused by DDIs and DDIs are also associated with longer ICU stay^{14,15}. All-in all, ADRs cause a huge financial burden with an estimated cost of \$16000 per hospitalization^{11,16,17}. Some adverse events are life threatening and even cause withdrawal of popular medications like siruvudine, astemizole etc. from the market thus leading to futile research overheads¹⁸. The Food and Drug Administration (FDA), the U.S agency responsible for regulating the safety of medications, medicinal supplements, and food items, reckons drug-drug interaction as a critical factor in the benefit-risk assessment of a drug during development and regulatory review, and has created a database, the FDA Adverse Event Reporting System (FAERS), which contains worldwide adverse event data¹⁹. The number of adverse event reports received and processed by the FDA increases marginally every year as indicated by the Graph 1. The fact that the percentage of persons using prescription drugs also reflects an increase in persons taking multiple drugs multiplies the gravity of the situation, as per Graph 2.

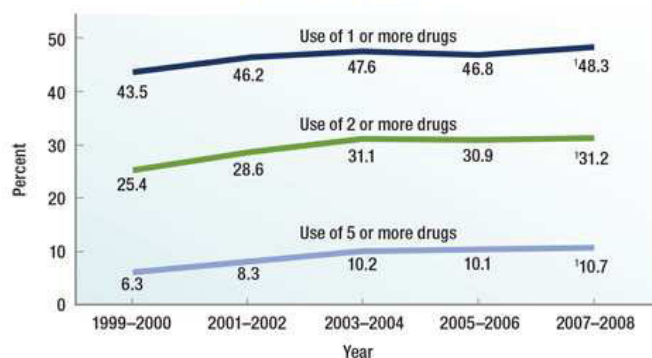
Graph 1
Number of reports of Adverse Events per Year¹⁹



The above graph illustrates the number of reports received (solid bars) and entered (checkered bars) into FAERS by type of report since the year 2000 until the end of 2010.

Graph 2
Trends in prescription drug usage²⁰

**Trends in the Percentage of Persons Using Prescription Drugs:
U.S., 1999-2008**



¹ Significant linear trend from 1999-2000 through 2007-2008.
note: Age adjusted by direct method to the year 2000 projected U.S. population.
source: CDC/NCHS, National Health and Nutrition Examination Survey

The importance of excavation of DDIs increases as more and more drug gets introduced in market.

EPIDEMIOLOGY OF DRUG INTERACTIONS

Epidemiology is a branch of medical science that deals with the patterns, distribution, and control of disease in a defined population. In the current case studies, emphasis is given to oncology, HIV treatment, and drug-drug interactions in the elderly as these are identified as groups where comorbidities, or the presence of two or more medical conditions in addition to an initial diagnosis, are treated. ADRs are found to be higher with Combination Therapy than in Monotherapy which indicates potential DDIs²¹. Rate of DDIs from other studies is also explored to understand rates and patterns of interactions.

CASE STUDIES FROM LITERATURE

(i) Antiretroviral/ HIV

HIV related morbidity and mortality has been considerably reduced by the triple combination antiretroviral therapy²². Antiretroviral therapy (ART) is widely used in HIV infection treatment and in majority of these cases; polypharmacy is required for treatment as the patients will have comorbidities. A DDI study was conducted at New York City HIV Specialty Clinics with 550 patients who were prescribed an average of 6 medications²³. Of these, 14% showed at least one DDI. Oshiyoka et.al conducted study among HIV infected children and found that 280 patients

were at risk of 596 DDIs²⁴. Another study in a Swiss HIV Cohort involving 1497 patients reported that 68% of patients had at least one DDI²⁵. This involved mainly central nervous system drugs (49%), cardiovascular drugs (45%), and methadone (19%). Clinically significant DDIs of 41.2% were reported among 153 randomly selected patients in a 2006 antiretroviral therapy study²⁶. A Kenyan study among 334 patients receiving ART reported a 33.5% DDI rate²⁷. It is reported that patients with age 42 and above are more prone to DDI²⁸. Other factors posing high risk of DDIs by this study are presence of more than three comorbidities, administration of more than five non-ART agents and treatment with more than four ART medications. Some other studies have stressed the need of therapeutic drug monitoring in ART²⁹. Another study reiterated the fact that DDIs increased with age and taking ART along with other medications³⁰. A study at the University of Liverpool has identified polypharmacy and age as key factors increasing DDIs³¹. The analysis indicates that the potential of DDIs increases with age and greatly depends on the number of medications.

(ii) Oncology

Psychotropics are often prescribed with other drugs to cancer patients due to preexisting psychological disorders and treatment related anxieties³². The patients are also prescribed supportive medications along with cytotoxic drugs³³. Patients in oncology clinics are usually treated for nausea and distress along with other symptoms³⁴. The number of drugs prescribed is higher in these cases, and so is the chance of DDIs. Studies in the field of cancer related nausea and distress report a 44.8% rate of DDI considering 440 medicinal combinations. 250 potential drug interactions were identified among 115 patients, of which 31% showed at least one DDI, the most common interaction being between warfarin and phenytoin³⁵. A South Indian study among 75 patients indicated 213 drug interactions of which 6.1% were DDIs among anti-cancer drugs and 6.5% were between anti-cancer drugs and medications for other co-morbidities³⁶. A study in metastatic

breast cancer (MBC) found the patients to be under risk for drug interactions due to the heavily pretreated nature of the disease and narrow therapeutic window³⁷. Two oncology patients treated for DDIs died among the hospitalized patients for treatment of DDIs³⁸. Analysis of the studies indicate that cancer patients have a higher chance of being prescribed a large number of drugs irrespective of age, and the higher the number of drugs, the more the number of potential DDIs, which can even be fatal.

(iii) Elderly population

Patients in upper age groups will have comorbidities and are another group which demands DDI study. Studies indicate that hospital admissions in elderly patients have resulted from known DDIs, many of which can be avoided if identified⁹. Research has also shown that DDIs increase with age^{39,40}.

Table 1
Distribution of patients exposed to potential drug-drug interactions, attendance in primary care³⁹

Age	Number (%) of patients exposed to drug – drug interactions (n=521)			
	Major	Moderate	Minor	Total
45-59	37 (37.0)	134 (36.8)	19 (34.6)	193 (36.6)
60-69	35 (35.0)	118 (32.0)	22 (40.0)	176 (33.4)
70-79	18 (18.0)	79 (21.6)	10 (18.2)	108 (20.5)
80-94	10 (10.0)	35 (9.6)	4 (7.2)	50 (9.5)
All	100 (19.2)	366 (70.2)	55 (10.6)	521 (100.0)

A study among Brazilian elderly indicated that 26.5% of the elderly population included in the study was prescribed medications involving DDIs with 64.4% of the women and 50.75% of the men being affected⁴¹. Patients 70 and older showed more DDI episodes with more medications prescribed⁴². DDIs among cardiology patients also increased with age⁴³.

Table 2
DDI rate in cardiology based on age⁴³

Age(Years)	Patients: n(%)
<=30	25(6.25)
31-45	64(16)
46-64	115(28.75)
>=65	196(49)

Studies have shown that DDI increases with age even in outpatients⁴⁴

Table 3
Annualized ambulatory visits involving clinically important DDIs⁴⁴

Age	Visit rate
<25	0.44
25-44	0.59
45-64	6.07
65-74	38.45
>74	70.12

An Iranian General Hospital study indicated increase in DDIs due to age and number of prescribed drugs⁴⁵. Age related changes and polypharmacy have been identified as part of the six reasons for DDIs among the elderly⁴⁶.

Factors Affecting Drug Interactions⁴⁶

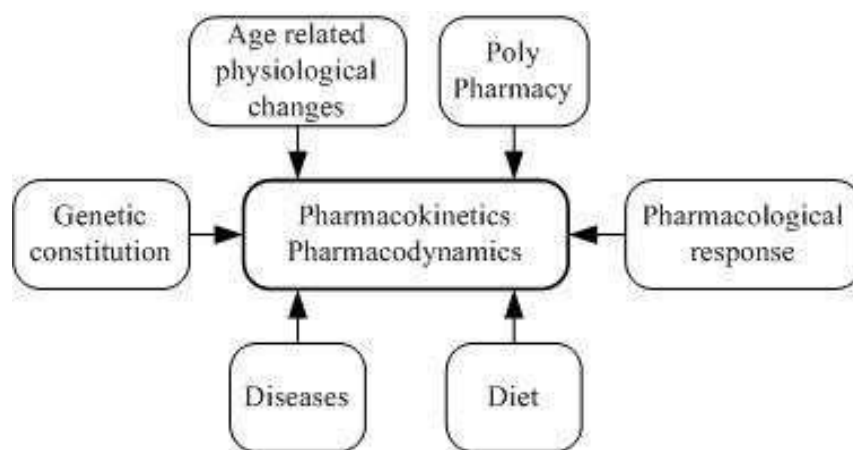
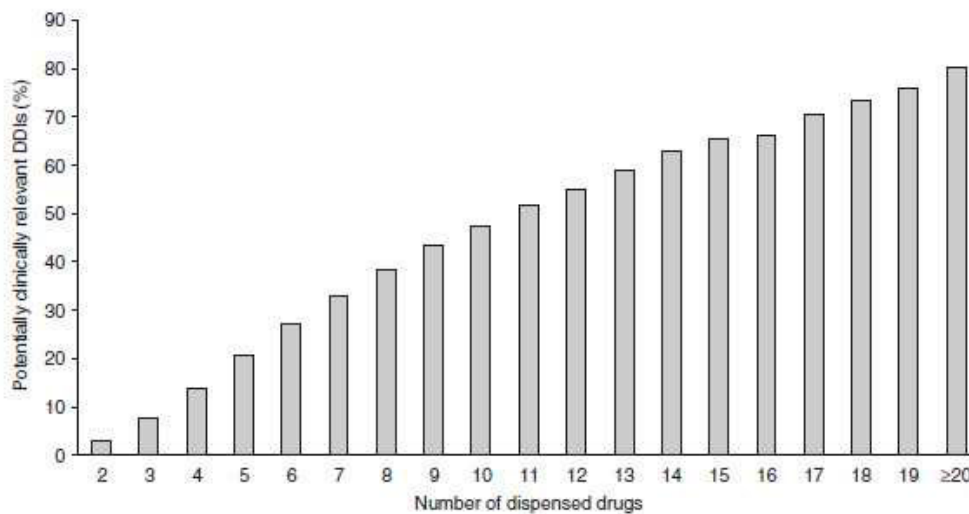


Figure 1
Factors Affecting Drug Interactions

There is little that science can do to age-related physiological changes, genetic constitution pharmacological responses and diseases in terms of drug interactions. Diet can be controlled to avoid interactions. It is the polypharmacy factor or multiple drug usage that drug-drug interactions studies have to take care of. Johnell did an extensive study regarding effect of polypharmacy usage in the elderly. The study indicates a direct correlation between number of drugs used and clinically relevant Type C and Type D DDIs⁴⁷.

Graph 3
Relation between DDIs and number of prescribed drugs.⁴⁷

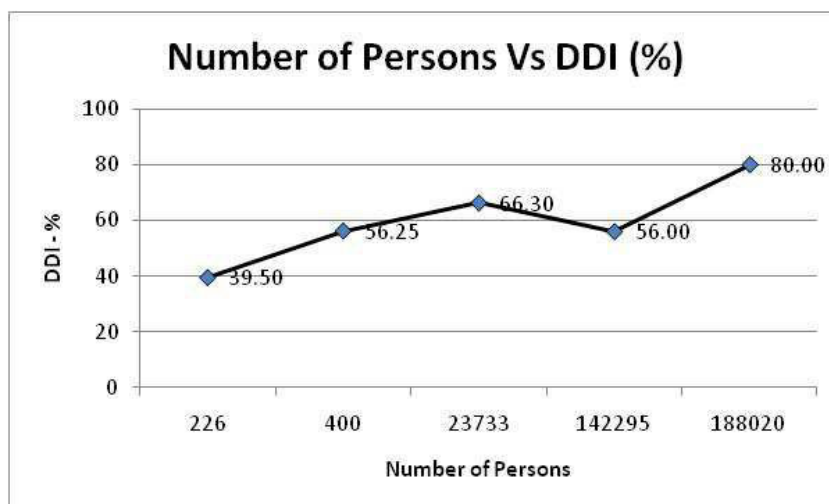


Prevalence of potentially clinically relevant Type C drug-drug interactions (DDIs) as a function of number of dispensed drugs among 630 743 people aged ≥75 years from the Swedish Prescribed Drug Register, 2005⁴⁷. A more thorough study based on each type of Adverse Drug Reaction as done in the case of diabetes patients is required to be performed in groups with comorbidities for further analysis of reasons underlying DDIs⁴⁸.

(IV) Other Case Studies.

The percentage of DDIs from other case studies based on cohort size is presented below in the form of a graph.

Graph 4
Percentage DDI for Number of Persons^{2,42,49,50,51}



When the number of persons increases, there will be more drug combinations and more chance of DDIs. The graph clearly indicates the necessity of large cohort and more general study to identify potential DDIs.

CONCLUSION

Age related factors, and use of multiple drugs has been found to be the reasons for drug-drug interactions. In addition large cohort studies are necessary to identify potential DDIs. The use of effective software is also necessary to combat the problem of polypharmacy prescribing.

Pharmacovigilance can be considerably improved using identification of novel DDIs. Sources of more general nature like the Spontaneous Reporting Systems can be used to find potential drug-drug interactions, as these are sources of data of a more general nature.

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