Chapter 2

LITERATURE REVIEW

Contents

2.1 Epidemiology of Drug-Drug Interactions

Epidemiology is a branch of medical science that deals with the patterns, distribution, and control of a disease in a defined population. In the current case studies, emphasis is given to oncology, HIV treatment, and drug-drug interactions in the elderly. ADRs are found to be higher with combination therapy than in monotherapy which indicates potential DDIs [54]. Rate of DDIs from other studies is also explored to understand rates and factors affecting interactions.

2.1.1 Case Studies

Epidemiology survey is conducted to find patterns of DDIs. The group is selected which were identified as cohorts where, comorbidities, or presence of two or more medical conditions in addition to an initial diagnosis, are treated.

a. Antiretroviral/HIV

HIV related morbidity and mortality have been considerably reduced by the triple combination antiretroviral therapy [55]. 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 medications [56]. Of these, 14% showed at least one DDI. Another study in a Swiss HIV cohort involving 1497 patients reported that 68% of patients had at least one DDI [57]. 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 study [58]. A Kenyan study among 334 patients receiving ART reported a 33.5% DDI rate [59]. It is reported that patients aged 42 and above are prone to more DDIs [60]. Other factors posing high risk of DDIs by this study were 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 ART [61]. Another study reiterated the fact that DDIs increased with age and taking ART along with other medications [62]. A study at the University of Liverpool has identified polypharmacy and age as key factors increasing DDIs [63]. The analysis indicates that the potential of DDIs increases with age and greatly depends on the number of medications.

b. Oncology

Psychotropics are often prescribed with other drugs to cancer patients due to pre-existing psychological disorders and treatment related anxieties [64]. The patients are also prescribed supportive medications along with cytotoxic drugs [65]. For example, patients in oncology clinics are usually treated for nausea and distress along with other symptoms [66]. 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 when 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 Warfarin and Phenytoin [67]. 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-morbidities [68]. A study in metastatic breast cancer (MBC) found the patients to be under risk for drug interactions due to the heavily pre-treated nature of the disease and narrow therapeutic window [69]. Two oncology patients treated for DDIs died among the hospitalized patients for treatment of DDIs [70]. 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 higher the number of potential DDIs, which can be fatal.

c. 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 identified [11]. Research has also shown that DDIs due to ADRs in elderly patients is highly significant (Table 2-1) [71], [72].

Table 2-1 Distribution of patients exposed to potential Drug-Drug Interactions, attendance in primary care [71]

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 affecting 64.4% of the women and 50.75% of the men [73]. Patients of age 70 and older showed more DDI episodes as more medications were prescribed [74]. DDIs among cardiology patients also increased with age (Table 2-2) [75].

Table 2-2 DDI rate in cardiology based on age

Age (Years)	Patients: n (%)
$\leq$ 30	25 (6.25)
31-45	64 (16)
46-64	115 (28.75)
$\geq$ 65	196 (49)

Studies have shown that DDI increases with age even in outpatients (Table 2-3) [76].

Table 2-3 Annualized ambulatory visits involving clinically important DDIs

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 drugs [77]. Age related changes and polypharmacy have been identified as one of the six reasons for DDIs among the elderly (Figure 2-1) [78].

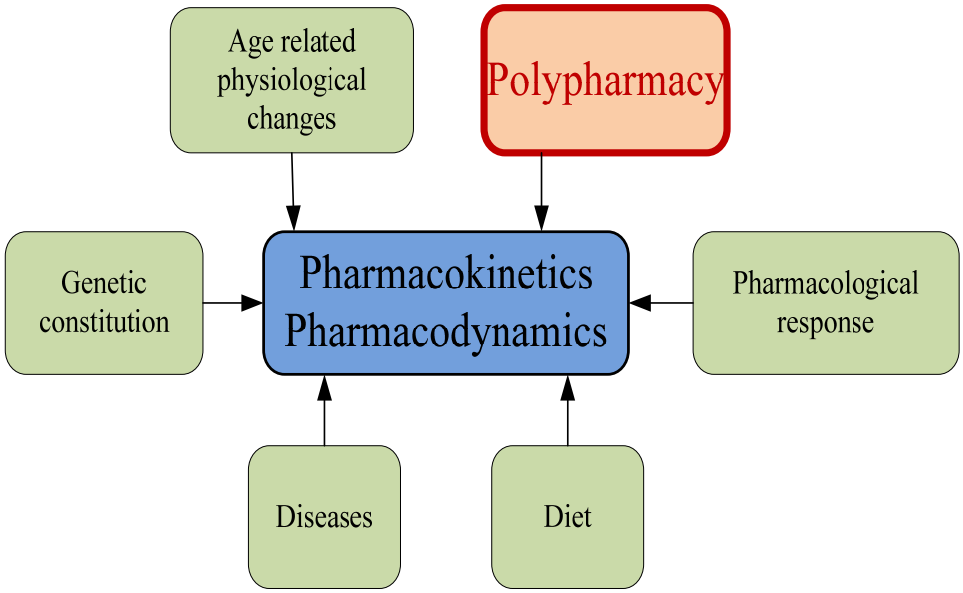

Figure 2-1 Factors affecting drug response and predisposing to DDIs in the elderly

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 of the effects of polypharmacy usage in the elderly. The study indicates a direct correlation between the number of drugs used and clinically relevant Type C and Type D DDIs (Figure 2-2, Figure 2-3) [79].

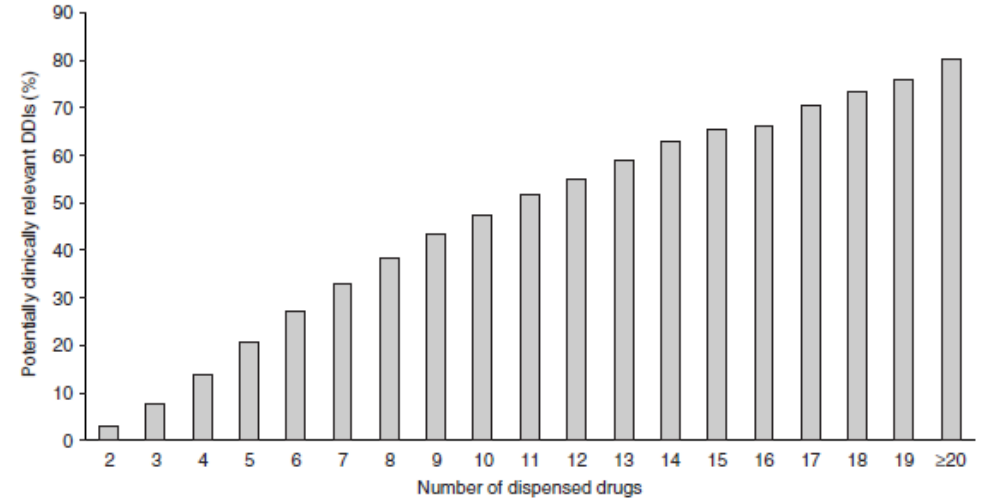

Figure 2-2 Number of drugs and clinically relevant Drug-Drug Interactions

Prevalence of potentially clinically relevant Type C DDIs as a function of number of dispensed drugs among 6,30,743 people aged 75 years and above from the Swedish Prescribed Drug Register (Figure 2-2) [79].

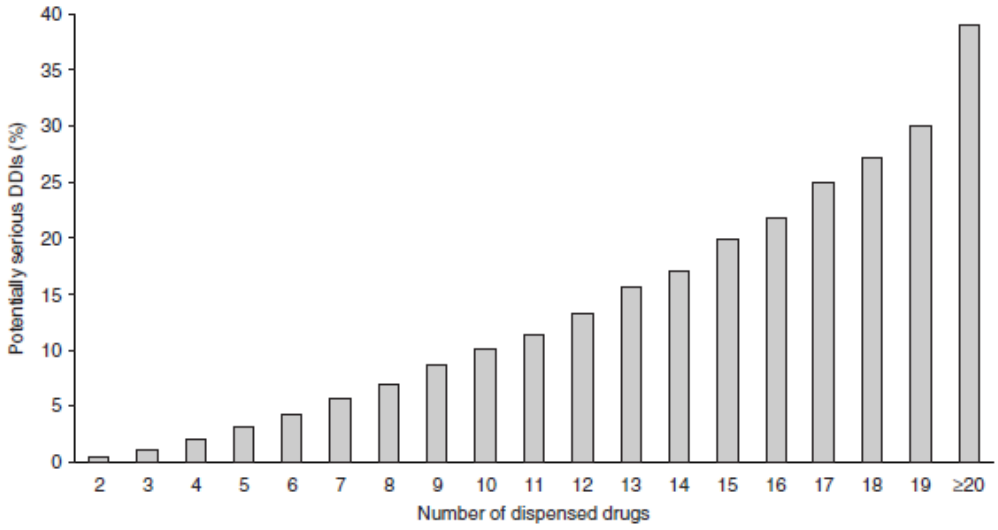

Figure 2-3 Serious Drug Interactions depending on number of drugs

Prevalence of potentially serious Type D DDIs as a function of number of dispensed drugs among 6,30,743 people aged 75 years and above from the Swedish Prescribed Drug Register (Figure 2-3) [79].

d. Statistics From Other Case Studies

The rate of drug interactions from other case studies (Table 2-4) clearly indicates a directly proportional relationship between DDI rate and cohort size. That is, larger the size of the population studied, the higher the number and types of drugs involved and the more likely it is for drugs to interact.

Table 2-4 Drug Interaction statistics from different case studies

No	Type	% of DDI	Number	Year	Reference
1	Antimicrobial drugs	39.5	226	2011	[80]
2	Cardiothoracic ICU	56.25	400	2010	[81]
3	Primary care	66.3	23733	2012	[74]
4	General	56	142295	2007	[82]
5	Inpatient	80	188020	2004	[83]

2.2 Contemporary Research

Microdosing has been used as a method to predict potential DDIs using volunteers [84]. The *in vivo* method is implemented by administering sub-pharmacological new chemical entity (NCE) micro doses to human volunteers. The subsequent pharmacokinetics is extrapolated for higher doses [85], [86]. This involves a risk element since reactions even in small doses can cause hazards. Regulatory authorities demand very less safety toxicology data before further studies prelude to market launch [87]. In addition, pharmacovigilance demands minimum patient exposure before product marketing.

A number of data mining algorithms are used to identify ADRs [88], [89], [90], [91]. These algorithms use SRS populations to interpret ADR rates.

The FDA drug labels have also been mined to find ADRs [92]. All these methods are useful in finding ADRs of individual drugs, but not DDIs. Also, these methods cannot predict new ADRs due to drug interactions. These applications analyse adverse reactions involving bivariate relations, i.e. a particular drug and its adverse event, but fail to excavate interactions between multiple drugs.

Pharmacokinetic computer programs are used to mine potential DDIs in treating infectious diseases [93]. Myopathy related DDIs are predicted and assessed using electronic medical records [94]. But all these methods are specific to a group of drugs or medical conditions and lack generality.

Whenever a drug interaction is reported, pharmaceutical and biomedical research is conducted on the issue and articles are published. These articles are identified as sources for finding DDIs. Text mining methods have also been implemented to identify DDIs from pharmacological documents and biomedical texts [95], [96], [97]. However these generally contain interactions of specific group of drugs or disease conditions. All these methods can explore existing, but not novel DDIs. Besides, the set of textual patterns proposed by pharmacologists, which forms the basis of textual searches, was found to be inadequate to identify many interactions [25]. As found in the survey of the epidemiology of DDIs in the previous section, studies concentrate on smaller cohorts, a particular disease, a number of interacting drugs administered concomitantly for a disease, or a particular age group. Biomedical and pharmacological documents also retain this property. It was also found that the number of DDIs increases with the number of medications administered together [74]. Moreover, the data in the previous section indicates higher DDI

rate for larger populations and hence requires a more general study (Table 2-4). All these shortcomings are to be overcome by a new method capable of identifying novel DDIs by cross matching a drug with every other drug.

2.3 Selection of the Methodology and Its Implementation

Association Rule Mining is reckoned as an efficient method for identifying relationships among variables in large databases. It was introduced by Agarwal et al. in 1994 and is based on the requirement to analyse large amounts of supermarket basket data, which inspired the invention [98]. The method has been used for numerous applications ever since. Association Rule mining is used for customer targeting , e-commerce, quality improvement of production process, Network Event Analysis, and analysis of spatial data sets [47]–[52]. Negative association rules can also be mined using the methodology to find items absent in transactions and hence can be used for efficient inventory management [53]. Association rules in large biomedical/biological databases can be mined using this method. HIV-Human Protein Interactions, gene ontology, and gene expression databases have been mined using this method in order to explore association rules [99], [100], [101], [102]. Association Rule Mining was applied to find ADEs in HIV drugs, hospital inpatient data and even in hospital infection control [45], [46], [103], [104]. Medical records of Chinese medicinal formulae have been searched for association rules for the prevention and treatment of breast cancer [105]. All these are very large databases that demand very high computational capability.

Frequent itemsets have been mined using the Apriori algorithm [106]. In the first step, the algorithm generates the frequent itemsets. In the subsequent step, the database is scanned to find support count of the

corresponding itemsets. Apriori algorithm has been identified as an efficient method for mining association rules and can also be used for multilevel association rule mining in large databases [107], [108]. Almost all the applications mentioned in the previous paragraph use the Apriori algorithm.

Systematic and random samplings are used for Association Rule Mining, using the Apriori and FP-growth algorithms, and analysis indicates that different sampling methods can be efficiently used and behave similarly in terms of accuracy [109].

The AIS, DHCP, and Partition algorithms have been compared to the Apriori algorithm and Apriori was determined to be the best among the four [110]. The number of association rules generated by the Apriori algorithm was larger for all confidence and support levels and the margin improved considerably as the number of transactions increased (Figure 2-4, Table 2-5).

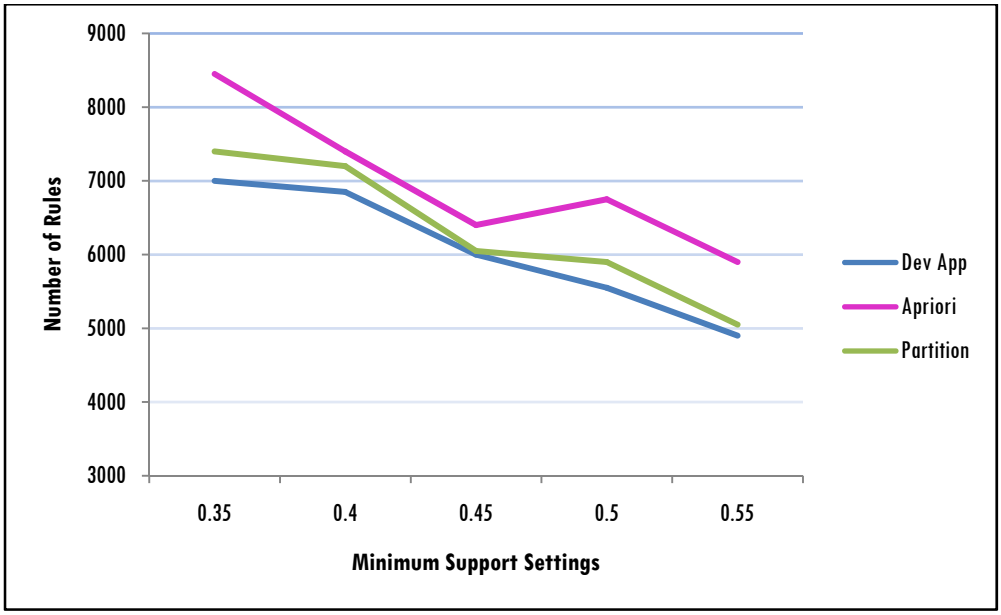

Figure 2-4 Apriori Performance Comparison

Table 2-5 Performance Comparison of the Apriori

	Data set 1	Data set 2	Data set 3
No. of transactions	120,000	400,000	750,000
No. of items	420	557	682
Max items/ transaction	18	26	38
Min items/ transaction	5	7	11
Support %	0.35%, 0.40 %, 0.45%, 0.50%, 0.55%	0.35%, 0.40 %, 0.45%, 0.50%, 0.55%	0.35%, 0.40 %, 0.45%, 0.50%, 0.55%
Confidence %	0.40%, 0.47 %, 0.55 % 0.60%, 0.65%	0.40%, 0.47 %, 0.55 % 0.60%, 0.65%	0.40%, 0.47 %, 0.55 % 0.60%, 0.65%
Avg # rules / FARMA	6262	6823	8118
Avg # rules / Apriori	7005	7597	9011
Avg # rules /Partition	6618	7107	8391

2.4 Pharmacovigilance

So far, the discussion has been regarding how the DDIs can be found. In the current section, the possible applicability of the DDIs identified using existing systems is discussed.

ADEs cause hospitalization, cost billions of dollars annually and is often fatal to patients [111], [112]. Pharmacovigilance intends to minimize Adverse Drug Events through minimum patient exposure before product marketing. Studies show that pharmacovigilance plays a crucial role in combating against DDIs due to the ever increasing range and potency of drugs [113]. DDIs pose additional and serious danger and must be identified and prevented. Drug Interaction Management demands tools to improve guideline quality [114]. A number of software tools have been developed to

cross match drugs to avoid DDIs during various stages of administration, using the currently known drug interactions. The Prescribing Optimization Method (POM) for polypharmacy prescription to the elderly, computerized pharmacy system for DDI checking, and High Speed drug interaction search system for clinical use, are all examples for DDI checking systems [115], [116], [117]. These tools can reduce the risk of ADRs to some extent [3]. Studies have also been conducted to compare standard tools for known DDI interaction checking by Perkins, Murphy et al. Five programs scored perfect sensitivity scores: DrugIx, ePocrates Rx, ePocrates Rx Pro, Lexi-Interact, and the Tarascon pocket Pharmacopoeia. Of these, the Mosbylx programs scored the highest in specificity (1.0). A comparison of the various tools is given in Table 2-6 [118].

Table 2-6 Comparison of various drug interactions checking software

Results by Program								
Program	**TP**	**FP**	**TN**	**FN**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
DrugIx (Handbook of Adverse Drug Reactions)	16	5	16	0	1.0	0.76	0.76	1.0
ePocrates Rx	16	2	19	0	1.0	0.9	0.89	1.0
ePocrates Rx Pro	16	2	19	0	1.0	0.9	0.89	1.0
iFacts (Facts and Comparisons Drug interactions)	14	1	20	2	0.88	0.96	0.93	0.91
Lexi-Interact (Lexi-Comp)	16	10	11	0	1.0	0.52	0.62	1.0
mobileMICROMEDEX	15	6	15	1	0.94	0.71	0.71	0.94
MosbyIx (Mosby's Drug Consult)	13	0	21	3	0.81	1.0	1.0	0.88
Tarascon pocket Pharmacopoeia (deluxe ed.)	16	10	11	0	1.0	0.52	0.62	1.0
Mean (SD)					0.96 (0.07)	0.78 (0.19)	0.80 (0.15)	0.97 (0.06)
Range					0.81-1	0.52-1	0.62-1	0.88-1
FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive.								

Adherence to drug label recommendations for certain drug interactions is stressed by some studies using data analysis of drug dispensing [119]. Research has found that data mining can be used to discover DDIs and unexpected ADRs to enable better drug safety [120]. Better pharmacovigilance can be achieved by using data mining tools for monitoring prescriptions or inpatient administration and adequate drug labelling, but these can only be made possible by the identification of potential novel DDIs.

2.5 Summary and Conclusion

Epidemiological study of drug-drug interactions indicates that they cause huge financial burden. DDIs are a common problem regardless of age and gender. The chances of DDIs increase with age and number of medications taken concomitantly. Since the elderly experience higher number of comorbidities, they take more medications and have more drug interactions. This again reiterates the increase in drug interactions due to multiple drug usage.

Percentage of DDIs increased when larger populations were involved in various studies, indicating that larger cohorts present more medicinal combinations, increasing the chance of DDIs, i.e., cross matching of drugs is to be made at a larger scale and more general cohort. Therefore, the data resource like FAERS which contain data collected worldwide and of a general nature can be used for the mining process.

As described in section 2.2, the current data mining methods like bivariate drug–AE identification and text mining are inadequate due to their specificity and inability to find new DDIs.

Based on the size of the database under consideration and the information to be mined (the association rules between drugs and their AEs from large data bases), Association Rule Mining can be used to find association rules using a suitable implementation of the Apriori algorithm.

Different existing drug safety tools can be more efficiently used only if novel DDIs are identified and this can substantially improve pharmacovigilance.