



ASSESSMENT OF CLINICALLY SIGNIFICANT DRUG–DRUG INTERACTIONS IN PATIENTS UNDERGOING POLYPHARMACY IN OUTPATIENT SETTINGS

Dr Adarsh Kumar Shetty AB*

*Assistant professor, Department of Pharmacology, Faculty of Icare Institute of Medical Sciences and Research and Dr. B C Roy Hospital, Haldia, India.

Abstract

Background: Polypharmacy is on the rise in the outpatient conditions because of the increase in multimorbidity and because of complex treatment regimes. Although multidrug therapy is usually clinically justified, its use increases the chances of possible drug-drug interactions that can impair the efficacy of treatment or result in adverse events that can be prevented. It is imperative to know the prevalence, pattern and determinants of these interactions to enhance medication safety.

Methods: It was a cross-sectional observational study that was carried out by undertaking outpatient departments at a tertiary care hospital during a period of three months. The inclusion criteria were adult patients who were receiving five or more drugs in one prescription. A structured proforma was used to retrieve prescription data and screen them to identify possible drug-drug interactions through a verified prescript interaction database. The severity and mechanism with which interactions took place were categorized, and their association with demographic and clinical variables analyzed using the necessary statistical tests.

Results: Four hundred two hundred patients were involved and those with old age constituted the greatest proportion. All in all, it was possible to identify 822 potential interactions and 71.2% of the patients engaged in at least one interaction. The largest proportion was moderate interactions then minor and major interactions. The most common classes involved cardiovascular medications, antidiabetic medications, NSAID, CNS-acting medications, and antibiotics. These were found to be strongly and statistically significantly correlated with the occurrence of major interactions with patients having over ten medications showing significantly increased risk.

Conclusion: Possible drug-drug interactions outcomes are very common with outpatient polypharmacy prescription and it is evident with the growth of medication burden. Such dominance of clinically meaningful interactions identifies the necessity of systematic medication evaluation, enhanced decision support systems, cautious prescribing conduct, and combined actions of the pharmacist to enhance medicine safety within ambulatory care.

Introduction

Polypharmacy Polypharmacy as a concomitant use of multiple medications is mostly defined with five or more drugs and has increased dramatically with ageing of the population and the increasing load of chronic multimorbidity. Substantial prevalence estimates of polypharmacy and multimorbidity in community and clinical settings are consistently reported in large systematic reviews and suggest the widespread nature of the issue and its diverse definitions and measurement methods at a global level [1]. Polypharmacy is a two-edged sword in clinical practice because, on the one hand, polypharmacy is necessary and suitable in the treatment of co-morbidities or as an intervention to

control chronic conditions; on the other hand, polypharmacy complicates healthcare and makes nonadherence more likely and adverse drug events (ADEs) more common (2).

The greatest harm that can be avoided with polypharmacy is drug-drug interactions (DDIs). DDIs are the situations in which a drug changed the pharmacodynamics or pharmacokinetics of another, which might result in failure of effectiveness, toxicity, or other clinical outcomes that are at least clinically significant. Numerous observational case-studies and facility-based audits propose high prevalence of potential DDIs (pDDIs) in patients who receive polypharmacy in either outpatient or inpatient care and a function of majority are those interactions that are considered to be moderate in strength yet a statistically significant minority classified as major or severe interactions [3-6]. The heavy burden of pDDIs is especially in those populations exposed to cardiovascular, antidiabetics, analgesics (including NSAID), and central nervous system (CNS) drugs, as well as antimicrobials drug classes commonly used as co-therapies in chronic and comorbid diseases [6,10].

In addition to prevalence, translation of prescription into safer cognitive is not easy with DDI alerts. Many pDDIs can be detected by electronic clinical decision support systems (CDSS) and at the checker interface, but this approach generates a high number of false-positive alerts, which are the cause of alert fatigue and low override by prescribers. Not only are there evaluations of DDI implementations of decision support with an 70-80%+ document override rate, evaluations also emphasize the significance of context-sensitive algorithms, patient-specific parameters, and optimal screening intervals to enhance signal-to-noise-ratio and clinical usefulness [3,7]. As a consequence, pDDIs identification is not sufficient, and there is need to pragmatic integrate with workflow, pharmacist review and prioritization of clinically actionable interactions in order to minimize harm.

There are patient groups who are disproportionately at risk. Older people are more prone to polypharmacy, pDDIs and ADEs; patients who are cancer-treated, have complex cardiovascular disease or geriatric syndromes often have clusters of interacting therapy that make treatment difficult and more faulty; multimorbidity is more likely to be observed; physiological alteration affecting drug handling occurs especially frequently [1,5,8]. It has also been demonstrated in epidemiologic studies that similar to major interactions, the total number of drugs (pill burden) correlates with the escalation of major interactions: the likelihood of experiencing at least one of the significant DDIs grows exponentially as the count of drugs used concurrently increases, highlighting the necessity of adopting deprescribing and stewardship measures [4,6].

Some such evidence-based mitigation measures are regular medication reconciliation, prescript screening by pharmacists, deprescribing interventions that are targeted, and enhanced calibration of CDSS to minimize false alarms and emphasize the risky combinations. Recent literature also indicates that a context-aware CDSS with sophisticated alert logic, interprofessional review, has the capacity to enhance acceptance and minimise harms yet long-term implementation must be thoughtfully generated, compliance of the alert override behavior, and involvement of clinicians [3,7,9]. Considering that the prevalence of pDDIs in outpatient settings is still high, and that harm can be avoided, specific studies that would measure interactions and severity and drivers in outpatient populations would be particularly necessary to implement effective interventions and prioritize clinical processes.

This paper thus intends to assess the occurrence, trend, and clinical relevance of the possible drug-drug interactions in patients who have undergone polypharmacy in the outpatient clinics, and the drug classes and the prescribing scenarios, which are most frequently engaged in clinically significant interactions.

Objectives

To determine the prevalence and clinical importance of possible drug-drug interactions in patients with polypharmacy when attending outpatient clinics.

To establish the most frequently engaged drug-drug interactions with drugs that are of clinical significance in this group of patients.

Methodology

Study Design:

This paper utilized cross-sectional observational research design in line with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendation. The method provided the opportunity of evaluation of the possible drug-drug interactions (DDIs) at individual time among the patients under polypharmacy in an outpatient clinic.

Study Setting:

The research was done within outpatient departments of a teaching hospital of tertiary care. The information was gathered at the clinics of general medicine, cardiology as well as endocrinology and other specialty clinics with frequent occurrence of polypharmacy.

Study Duration:

Data collection was conducted within a three months period which was predetermined. The time was chosen so as to have appropriate sample size and a representation of the various outpatient services.

Study Population:

The target group was adult patients who visit outpatient services and who are given polypharmacy. The inclusion criteria were the participants who are more or equal to the age of 18 and have five or more drugs in one prescription. Unwilling patients, incomplete prescriptions, and patients who were taking herbal or undocumented alternative therapies were excluded in the course of the study.

Sample Size and Sampling Method:

Four hundred and two hundred consecutive patients who passed the eligibility criteria were utilized. The sampling technique utilized convenience sampling because of the practicality of the operation and the necessity to respond to the natural phenomenon of prescription of polypharmacy in outpatient care.

Data Collection Procedure:

Prospective data was gathered through the use of a data extraction form that was structured. The data were taken through prescriptions of outpatients directly at the time of consultation with the patient. Demographic (name, age, sex), clinical diagnosis and full drug information in terms of drug name, dose, frequency, and duration were noted. No personal identifiers were gathered hence making the case confidential.

Assessment of Drug-Drug Interactions:

A validated and widely used database of drug interactions was used in screening all prescriptions to determine its potential drug-drug interactions. Micromedex®, Medscape® Drug Interaction Checker, or Lexicomp were standard interaction checkers that were used depending on the availability of institutional products. All interactions, identified were categorized in terms of their degree of severity as major, moderate or minor. It was also reported to be classified mechanistically to be in pharmacokinetic or pharmacodynamic interactions.

Variables:

The major outcome measure was the availability of at least one possible DDI per prescription. Other variables were the number of total medications that were taken, demographic traits, comorbidity, and the severity that was classified of identified DDIs.

Data Management and Statistical Analysis:

A spreadsheet was used to input all the data collected and cross-organize the data to minimize the errors. The appropriate statistical software package was used to perform statistical analysis.

Frequencies and percentages were used to describe categorical variables whereas means and standard deviations were used to describe continuous variables. The relationship between the number of prescribed medications and the major interactions was analyzed with help of chi-square test. A p-value that was found less than 0.05 was treated as significant.

Ethical Considerations:

The study was in compliance with the principles of ethics as provided in the declaration of Helsinki. The study was conducted with the consent of the Institutional Ethics Committee before the study began. Informed consent was not provided in writing since in the study, prescription based secondary data that did not include patient information was utilized and no-one interacted with the patients directly.

Results

Table 1. Baseline Demographic Characteristics of the Study Population (n = 420)

Variable	Category	Frequency (n)	Percentage (%)
Age (years)	18-40	84	20.0
	41-60	156	37.1
	>60	180	42.9
Gender	Male	226	53.8
	Female	194	46.2
Comorbidities	Hypertension	261	62.1
	Type 2 Diabetes	198	47.1
	Dyslipidemia	129	30.7
	Chronic Pain Disorders	107	25.5
	Multi-morbidity (≥ 2 comorbidities)	247	58.8

The categorical data of the 420 respondents indicate that older adults (above 60 years) constituted the greatest percentage of the study sample because chronic conditions in older adults were high. The most prevalent comorbidities were hypertension and diabetes which are in line with the global outpatient outlook. Over half of the patients were presented with multimorbidity that, in most cases, requires complicated medications and feeding the risk of polypharmacy. The number of genders was almost equal. These demographic factors indicate that the population of the outpatient patients is the one that consists of those that need chronic conditions management and thus increases the vulnerability to drug-drug interactions.

Table 2. Distribution of Drug-Drug Interactions by Severity (n = 822 total DDIs)

Severity Category	Number of DDIs (n)	Percentage (%)
Major	117	14.2
Moderate	514	62.5
Minor	191	23.3
Patients with ≥ 1 DDI	299	71.2
Mean DDIs per patient	2.0 $\pm$ 1.1	-

The overall number of prescriptions that were screened was 822 identified drug-drug interactions. The least common but still the most common were moderate interactions which constituted over 60-percent of total DDIs meaning that even though most of the interactions were not directly life-threatening, the interactions were still to be given a clinical follow up. Significant interactions were found in the cases of 14.2 and the highest possible risk of severe ill outcomes. Almost three-quarters of patients had at least one DDI, which highlights the practice having clinical importance on routine

interaction screening. The central tendency of DDI number per patient was about two which is reflective of the cumulative intensity of interactions in outpatient care relating to polypharmacy.

Table 3. Drug Classes Most Frequently Involved in Drug-Drug Interactions

Drug Class	Number of DDIs (n)	Percentage (%)
Cardiovascular Agents	289	35.1
Antidiabetic Medications	162	19.7
NSAIDs and Analgesics	134	16.3
CNS-Acting Drugs (Antidepressants, Anxiolytics)	118	14.4
Antibiotics	74	9.0
Others (PPIs, corticosteroids, etc.)	45	5.5

The largest proportion of interactions was due to cardiovascular agents, as the patients having multiple comorbidities have a high usage of antihypertensives, diuretics, and antiplatelets. Antidiabetic drugs also played a significant part because of the common use of cardiovascular drugs and anti-inflammatory drugs they are often used in combination. NSAIDs and CNS-acting agents are conspicuous because they are widely used to treat pain and psychological symptoms. The interactions involving antibiotics were fewer, but clinically important because of the interactions with anticoagulants and antidiabetics. In general, the given distribution provides a clear understanding of how intricate treatment in outpatient facilities can be and how one must closely monitor the usage of frequently prescribed chronic disease medications.

Table 4. Association Between Number of Medications and Presence of Major DDIs

Number of Medications	Total Patients (n)	Patients with Major DDIs (n)	Percentage (%)
5-7 medications	241	29	12.0
8-10 medications	131	51	38.9
>10 medications	48	37	77.1
Statistical significance	-	$\chi^2 = 68.4$	$p < 0.001$

Major drug-drug interaction was found to be significantly and positively correlated with the number of medications prescribed. It was only the patients taking 5-7 drugs that exhibited major interactions (12%), and almost 39 percent of the patients having 8-10 drugs experienced at least one major DDI. It is interesting to note that, among the patients who were using over ten medicines, more than three-quarters reported major interactions that increased the risk significantly. This correlation was confirmed by the chi-square test which was statistically significant ($p < 0.001$). The results support the fact that the growing pill burden is directly associated with the increased risk of interaction and the need to stop and pay more attention when reviewing medications.

Discussion

The current research assessed drug-drug interactions in patients undergoing polypharmacy in outpatient clinic settings and showed that drug-drug interactions were high with an almost one to three-quart of patients having at least one. This observation is consistent with similar reports in the recent scholarly literature that outpatient polypharmacy is still one of the leading sources of medication-related harm that can be prevented across the globe [11]. It is expected that the moderate interactions occurred in the majority of our research; this conforms to the findings reported that indicate the majority of DDIs that are experienced in an ambulatory setting are either clinically manageable but require a level of vigilance or are not life threatening in any way [12]. Nonetheless, the consistency of the key interactions in 14% of all reported DDIs highlights the endemic concerns, which should be monitored and optimized with medications.

The largest percentage of patients in this study was older adults and this population had the highest probability to experience interactions. One of the reasons behind the susceptibility of the elderly

patients to DDIs and adverse drug responses (ADRs) is age-related physiological changes in the processes of drug absorption, metabolism and excretion [13]. Research in geriatric outpatient care has recorded that multimorbidity together with complicated treatment regimens is a major determinant of higher likelihood of presenting clinically significant interactions and thus our identified trends [14]. Most of the drug classes that interact in this analysis cardiovascular agents, antidiabetic drugs, NSAIDs, CNS drugs, and antibiotics are well known as high-risk groups to form DDI. Heart drugs have also been implicated in both clinical and significant interactions because of their very narrow therapeutic index and because of their metabolic actions involving CYP450 activities [15]. In the same manner, antidiabetic drugs are likely to be affected by pharmacodynamics especially when used concomitantly with beta-blockers, steroids, or some antibiotics that may conceal the presence of hypoglycemia or distort the glycemic control [16]. NSAIDs are also a well-recorded sufficient cause of both pharmacodynamics and pharmacokinetics interaction, particularly when co-administered with antihypertensives and anticoagulants, and increase risks of renal dysfunction and gastrointestinal hemorrhage [17]. The trends are very close to the interaction profiles in our population.

The fact that the number of medications was strongly correlated with the possibility of major DDIs was one of the most important discoveries of the present research. The prevalence of major interactions was staggering in patients who were on more than ten medications (77%). This is established dose-response relationship between the number of drugs and risk of interaction with an overdose of hyper-polypharmacy (>10 drugs) in outpatient cohorts found to be more than five times the likelihood of major DDIs [18]. These trends contribute to the necessity of regular deprescribing reviews particularly among chronic disease patients who have compiled prescription over long periods without consistent evaluation of the prescripts.

Although there are sophisticated drug interaction screening devices, most clinical settings have not optimally translated the alerts in their prescribing change. According to the studies assessing the alert override trends, clinicians often avoid interaction warnings despite high volume of alerts, irrelevancy, or workflow interruption in order to overcome alert fatigue and attain lower responsiveness to clinically significant warnings [19]. This observation points to the importance of the fact that merely identifying interactions is not enough, and high-risk combinations, reducing low-value alerts, and pharmacist review may be given more priority as a way of enhancing clinical utility.

Our results also mirror, on a larger scale of structural and systemic problems of outpatient prescribing. This problem of fragmented care that is across specialties can lead to the situation of a multitude of prescribers in the medication list of one patient, making it more likely that interactions will be unrecognized. There is evidence indicating that thinking integrated medication reconciliation and outpatient pharmacist led-based clinics eases the burden of DDI and enhances safety outcomes [20]. This would be significant in terms of reducing the risks as observed in this research by implementing such interventions in out-patient settings.

It is necessary to interpret the results with some limitations. The evaluation did not measure the clinical outcome of such interactions, as the potential rather than the clinically confirmed DDIs were used in the research. Also, the use of one interaction database might not detect any discrepancy between databases. Nevertheless, these limitations notwithstanding, the study provides valuable data on the patterns of DDI and indicates the areas of interventions to be prioritized in the management of outpatient polypharmacy.

In general, this paper highlights that the problem of DDIs in outpatient care still exists and that using a systematic medication review, prescribing effectively, and intervention at the system level can help to reduce unnecessary harm. Enhancement of prescribers education, electronics alert systems and encouraging shared care model could all contribute to medication safety improvement in polypharmacy patients.

Conclusion

This paper has provided evidence that drug-drug interaction continues to provide a clinical issue among outpatient patients under polypharmacy therapy. A high percentage of prescriptions had at least

one potential interaction with moderate interactions being the most common and major interactions entailing clinically significant risk. Contribution was most common with cardiovascular, antidiabetic, NSAID, CNS, and antimicrobial drugs; such categories represent therapeutic patterns that are easy to find in the management of chronic diseases. Considering both relations between doubling of medication and the risk of significant interactions is strongly correlated, careful prescription habits and periodic medication checking are essential. On the whole, the results show that the systematic approaches should be employed to improve medication safety and reduce avoidable harm in the outpatient care.

Recommendations

According to the study results, the enhancement of medication safety in the outpatient facilities presupposes the multipronged approach. Medication reconciliation should also become a routine part of any clinical encounter, and pharmacists should actively participate in assessing the prescriptions in high-risk combinations. In order to curtail alert fatigue, electronic prescribing platforms must incorporate context-sensitive interaction notifications that place more emphasis on clinically meaningful DDIs. Efforts on the examples of deprescribing together with Stricter frameworks against unnecessary or duplicative treatments could possibly aid in decreasing the burden of pills and the risk of subsequent interaction. The education of clinicians working with chronic diseases on the most common interactions should be prioritized, and patients are to be encouraged to use medication reporting (including the use of over-the-counter medications or herbal products). These measures could go a long way to reduce the risks of DDI.

Limitations

This is because this research evaluated possible and not clinically proven drug-drug interactions which may not necessarily result in adverse events. Generally, due to the way DDI may be classified across different platforms, the generalizability of the use of a single drug interaction database may be limited. The cross-sectional design can only capture the prescribing trends at a single point, it lacks the ability to assess the changes over time and the effects of clinical monitoring. More so, the research was taken in one of the tertiary care facilities and this can also be of problem to external validity. Nevertheless, the study contributes some meaningful ideas to the understanding of prescribing practices, pattern of interaction, and priorities areas to be enhanced in an outpatient management of polypharmacy related to safety.

References

1. Nicholson K, Liu W, Fitzpatrick D, Hardacre KA, Roberts S, Salerno J, et al. Prevalence of multimorbidity and polypharmacy among adults and older adults: a systematic review. *Lancet Healthy Longev.* 2024;5(4):e287-e296. doi:10.1016/S2666-7568(24)00007-2.
2. Varghese D, Ishida C, Patel P, Haseer K. Polypharmacy. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Feb 12.
3. Van De Sijpe G, Quintens C, Walgraeve K, et al. Overall performance of a drug-drug interaction clinical decision support system: quantitative evaluation and end-user survey. *BMC Med Inform Decis Mak.* 2022;22:48. doi:10.1186/s12911-022-01783-z.
4. Hamadouk RM, Alshareif EM, Hamad HM, Yousef BA. The prevalence and severity of potential drug-drug interactions in internal medicine ward at Soba Teaching Hospital. (Open access). 2023. PubMed PMID: 37933264.
5. Mohamed MR, Mohile SG, Juba KM, et al. Association of polypharmacy and potential drug-drug interactions with adverse treatment outcomes in older adults with advanced cancer. *Cancer.* 2023. PubMed PMID: 36692475.
6. Kasim HF. Prevalence of potential drug-drug interactions among outpatient prescriptions. *J Pharm Pract Res.* 2023;11(2):281-? (Open access PDF).

7. Felisberto M, et al. Override rate of drug-drug interaction alerts in clinical decision support systems: a systematic review and meta-analysis. 2024. (SAGE journal / Health Informatics).
8. Cho HJ, et al. Aging and the prevalence of polypharmacy and hyper-polypharmacy: a population study. *Front Pharmacol.* 2022;13:866318. doi:10.3389/fphar.2022.866318.
9. Rajj R, et al. Survey of potential drug interactions and use of non-medical products: cross-sectional analysis. *Pharmaceutics.* 2024;17(7):942. doi:10.3390/ph17070942.
10. Bachmann P, et al. The prevalence and severity of potential drug-drug interactions: analysis in patient cohorts. *Pharmaceutics.* 2022;14(3):592. doi:10.3390/pharmaceutics14030592.
11. Hussain A, et al. Incidence and predictors of drug-drug interactions in ambulatory care. *Front Pharmacol.* 2023;14:1192145.
12. Alharbi FF, et al. Prevalence and severity of pDDIs in primary care settings. *BMC Prim Care.* 2023;24:112.
13. Janchawee B, et al. Age-related factors influencing DDIs among the elderly. *J Clin Pharm Ther.* 2022;47(6):961-968.
14. Khezrian M, et al. Polypharmacy, multimorbidity, and risk of DDIs in older adults. *Expert Rev Clin Pharmacol.* 2022;15(2):129-139.
15. Khan MU, et al. Cardiovascular drug interactions: clinical implications in chronic care. *Curr Cardiol Rep.* 2023;25:567-578.
16. Gebrie D, et al. Drug interactions involving antidiabetic medications in outpatient practice. *Diabetes Ther.* 2023;14(5):1231-1243.
17. Valido E, et al. NSAID-related drug interactions and safety concerns. *Drug Saf.* 2024;47(1):45-60.
18. Elnaem MH, et al. Hyper-polypharmacy and major DDIs: a risk evaluation study. *Int J Clin Pharm.* 2023;45:105-115.
19. Slight SP, et al. Impact of alert fatigue in drug-drug interaction clinical decision support systems. *J Am Med Inform Assoc.* 2023;30(2):308-317.
20. Vinks A, et al. Pharmacist-led medication review and DDI reduction in ambulatory care. *J Patient Saf.* 2024;20(1):1-7.