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A Review on Impact of Drug Utilization Study on Drug-Drug Interactions in the Cardiolody Department

M.RangaPriya*, Nancy Sinha, Merin Kurian, Merlin K Reji,Nandhini.P.M
*SwamyVivekanandha **College** of Pharmacy, Tiruchengode,Dr.MGR Medical University, Tamilnadu, India*
**Author for Correspondence: Dr.M.RangaPriya, M.Pharm., Ph.D., Professor & Head, Dept. Of Pharmacy Practice, SwamyVivekanandha College of Pharmacy, Tiruchengode, Tamilnadu – 635207*

Abstract
Drug-drug interactions (DDIs) are the major source of medication error, particularly in older patients because of polypharmacy. Polypharmacy has been associated with increased adverse drug reactions, increased health-care costs and reduced functional capacity in older people. Patients with cardiovascular disease are at high risk of drug-drug interactions. The Drug utilization study evaluates the present and future trends of drug use pattern, detection of early signals of irrational drug therapy, estimation of drug expenditures, make interventions to improve drug use and quality control of drug use. DUS is a useful strategy for a cost effective healthcare and helps in rational drug therapy. This review reveals the influence of DUS to reduce the DDIs and ADRs, intensify the safety and efficacy of drug therapy and thereby improves the quality of life.

Keywords*: Drug utilization study, Polypharmacy, Drug-drug interactions, Rational drug therapy, Comorbidities*

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I. Introduction:

A drug-drug interaction (DDI) is a pharmacokinetic or pharmacological response of one medication on the other medication that alters the known or unknown effects of each agent alone. A DDI may end up in changing either drug effectiveness or drug toxicity by bothone or more of the interacting therapy.[1]Drug utilization pattern is a solid investigationaltool to evaluate the present fashion of usage of drug, appropriate prescriptions, and reducing drug-drug interaction and preventing of adverse drug reaction.[2]DUS estimates the safety and rationality of drug therapy. It produces a positive impact on the prescribing health care professionals and improve the pattern of prescribing by the physician and help them to change the treatment strategies whenever needed, identify and make an appropriate decision for safe and cost-effective therapy.[3]Drug utilization studies favour the treatment of drug-related problems and the estimation of proper drug therapy. Understanding and managing the prescription pattern is the primary step toward the drug quality and safety of the patient.[2]

Cardiovascular diseases are the major cause of death all around the globe. Around 70% of deaths are due to non-communicable diseases such as cardiovascular diseases, cancer, and chronic respiratory disease.[4] As various studies showed that CVD patients are more often resulted in pDDI as compared to other diseases. The feasible reason behind the higher pDDI rate in CVDs may include old age, multiple drug therapy, and the pharmacokinetic or pharmacodynamic nature of medication employed in the cardiology department. Cardiovascular medications are most frequently involved in pDDI.[5] A broad dimension of concomitant disorders may complicate the therapy by further summing morbidity and mortality.[6] So multiple drugs at a time due to several multimorbidities turn out to be a hurdle to get appropriate therapy. This poly-pharmacy can lead to drug interactions which complicate the diagnostic results and leads to other unwanted consequences.[7] Drug-drug interaction is one of the major causes of adverse drug reaction (ADR) occurring in health centre and emergency department.[8] Drug-drug interactions constitute 6- 30% of all ADRs.[9]

PAST, PRESENT, AND FUTURE OF DRUG–DRUG INTERACTIONS

Over the last two decades, there is subsequent progress in DDIs, and in the upcoming years, it will become one of the greatest challenges in the health care system.[10] It started by the turn of the century as there was an international conference by the European Federation of Pharmaceutical Sciences, American Association of Pharmaceutical Sciences, and the US Food and Drug Administration (FDA) in 2000, stating that to analyse,

predict and manage the DDIs. It focused mainly on these topics like mechanistic consideration, in vitro evaluation, the prognosis from the in vitro data, the clinical study design, population pharmacokinetic analysis, manage the in vivo studies, and including the study of this.[11] The EMA guideline published in 2012, provides a clear explanation about the interaction potential of an investigational drug. This guideline was revised and updated in 2017. This update includes some additional points on basis of emerging scientific information (e.g. in the area of drug transporter).[12] In the present time, the alarming concern for DDIs is the prevalence of polypharmacy, usage of alternative medicines, people with multimorbidity, and older age over 65 years are at the greatest risk of DDIs. As it is the responsibility of the physician and the pharmacist to prevent unwanted DDIs as they can provide rational health care with proper therapy and counselling.[10] For future aspects, many experts suggested managing the DDIs by adjusting the dose or dosage regimen, paying more attention to pharmacodynamics interactions, and usage of biomarker monitoring.[11] Moreover, we can include the participation of racial and ethnic minorities because this group of people shows specific genetic polymorphism in their enzymes and transporters. The use of modelling and simulation provides a great deal to manage the risk of DDIs in individual patients. Apart from the scientific development, there is a need to increase relevant information for physician and pharmacist and to enhance their knowledge as well as patients and family members to reduce the incidence and prevalence of DDIs in day to day life.[10]

MECHANISM OF DRUG DRUG INTERACTIONS

It has both pharmacodynamic (PD) and pharmacokinetic (PK) mechanisms. [13] Pharmacodynamics (PD) interactions can be divided into three; interactions that take place at a single receptor site, interactions that occurs at a variety of receptor sites, and non-specific interactions mediated through unspecified site of action. [14] The mechanism of DDIs can be analysed by using an automatic computational method called MeSH.[15]The absorption, distribution, biotransformation or elimination of one or more drugs will get affected by Pharmacokinetic (PK) interactions. In pharmacokinetic and pharmacodynamic interaction, the two or more drugs will interact simultaneously. For example; Aspirin replaces warfarin from the plasma protein binding site and increases the warfarin level which is a pharmacokinetic interaction. In addition, the antiplatelet effect of aspirin and the anticoagulant effect of warfarin will potentiate each other at the pharmacodynamic level. [16]

POLYPHARMACY: A DEVIL IN DISGUISE

Polypharmacy is a title that first came into light in the medical literature about 150 years ago.[17] Nowadays polypharmacy has become a prominent challenge for the health care system.[18] Polypharmacy shall be defined as the concurrent use of multiple drugs by a single individual at a period.[17] But there is no particular standard definition for polypharmacy, whether it be categorized as appropriate or problematic. When a drug user is optimized, the prescription is evidence-based, which in turn improves the patient's health outcome and quality of life (QOL), which is termed as appropriate polypharmacy. However, when the increase in the incidence of interactions and adverse events (AEs) of multiple drug therapy affects the patient's safety, efficacy and rationality of therapy, this is termed as problematic polypharmacy. Despite the gain, polypharmacy is mainly considered to develop the risk of ADEs, drug-drug interactions, irrational prescribing, noncompliance to drug regimens, increased hospitalization and mortality in older people.[19] Polypharmacy commonly affects the older population due to their multimorbidity. Globally, the health burden of comorbidity is expected to increase steeply as a result of the developing number of elder people and a significant number of people living with multimorbidity.[20] Polypharmacy is correlated to many undesirable consequences.[11] The consequences are negative health outcomes, including mortality, falls, adverse drug reactions, increased length of the stay in the hospital, return to the hospital soon after discharge and cost-ineffective therapy.[20] Some authors have dictated polypharmacy as the usage of many drugs than therapeutically indicated. However, the term depends on a clinical judgment that is difficult to conduct in a large population. The pharmacoepidemiologyanddrug utilization study is a strict numerical gateway to define polypharmacy.[21] Poly-pharmacy indulges with irrationality in drug therapy and which increases the possibility of drug-drug interaction. In severe cases, DDI can lead to an adverse drug reaction, medication errors, and patient non-adherence to the treatment.[22] Polypharmacy plays a key role in drug interaction and leads to further complications.[23]

RELATIONSHIP BETWEEN ADVERSE DRUG REACTION (ADR) AND POTENTIAL ADVERSE DRUG INTERACTION

According to World Health Organization guidelines, adverse drug reactions are referred to as "noxious or unintended responses to medication which occur despite appropriate drug dosage for prophylaxis, diagnosis or therapy of the indicating medical condition". Potential adverse drug interactions (PADIs) were defined as more than one medication taken at a time before the index befall that put the patient at high risk for later adverse drug interaction.[19] Drug-drug interaction has both medication-specific and patient-specific factors.[24] Every

time a person follows a prescription drug there is a potency to cause an ADR. The potency develops with an increase in the number of concomitant medications being prescribed. So the potential drug interaction is the future reason for ADRs. Many studies have reported that drug-drug interactions (DDIs) may add up to 30% of unexpected adverse drug reactions (ADRs). Adverse DDIs can be avoided if discovered previously. It is unable to study DDIs before post-market approval. A causal relationship between drug-drug interactions and adverse reactions can be proposed by a new method called CARD (Causal Association Rule Discovery).[25] Adverse drug effects can also be related to drug-drug interaction. Estimation of adverse drug effects as well as the assessment of drug-drug interactions on their symptoms is a non-triform task that requires numerous experimental and clinical studies. Several studies developed a computational outlook for the prognosis of adverse effects that are evolved by drug-drug interactions.[26] As it is stated above, drug interaction occurs mostly in cardiac patients due to their multiple drug regimens and the influence of associated comorbidity. Every DDIs have differences in the medication at the initiation of interactions and when the concentration of medication is changed, from the same interaction it eventually leads to favourable or unfavourable effects. Several studies have reported that adverse drug reactions are the main cause of 0.5% to 2% of patients involved in ambulatory medicine and 4% to 10% of patients get intricate to hospitalizations According to studies, 1/3 of the adverse reactions is caused due to negligence and they should be able to prevent it. Data from various studies showed that 20% of the adverse effects are caused due to DDIs.[27]

II. Confounding Multimorbidity

DDI is a major concern in the treatment of patients presenting with cardiovascular diseases as most of the cardiac patients present with comorbid conditions leading to the prescription of multiple drugs. It has been observed that cardiac patients are more prone to drug interactions as compared to other patients.[28] Diabetes and hypertension occur concurrently and both conditions lead to impair cardiac autonomic control. Both HRR and HRV recovery was impaired in DM and HTN.[29] Hypertension and diabetes are commonly regarded as an independent predictors for heart disease.[30] Type 2 diabetes mellitus is a growing epidemic metabolic disorder associated with a spectrum of complications, with 2 to 4 folds higher incidence of cardiovascular disease and hypertension is another comorbidity with a 40% prevalence among patients. The existence of both DM and HTN is mainly the cause for metabolic syndrome, abdominal obesity, diabetic nephropathy, and advanced atherosclerosis. A study shows that about 60%–80% of people with type 2 diabetes die of cardiovascular complications, and up to 75% of specific cardiovascular complications have been attributed to high blood pressure. Moreover, hypertension is also a primary contributing factor to kidney failure and eye ailments in people with diabetes.[29] Hypertension is found to be a major contributor to heart disease, which starts to develop early in a chronic kidney failure. Diabetes is also a risk factor for heart disease through damage to blood vessels.[30] Obesity is a high prevalent chronic disease and the obese individuals are diagnosed with increased cardiovascular risk. Both the T2DM and/or HTN can impair the cardiac autonomic function in obese patients. Several comorbidities, such as type 2 diabetes mellitus (T2DM), arterial hypertension (HTN), dyslipidemia and obstructive sleep apnea syndrome, contributes to high cardiovascular morbidity and mortality in the obese patients.[3] The presence of multiple cardiac conditions in an individual was associated with age, sex, and race-ethnicity. Older patients and men were more likely to be in risk of multiple conditions.[31]

INFLUENCE OF POTENTIALLY INAPPROPRIATE PRESCRIBING (PIP)

Potentially inappropriate prescribing (PIP) refers to using medications in a state of affairs in which the risk of an adverse drug event (ADE) outweighs the clinical benefit, especially whilst more safer or effective options are to be had, and the omission of clinically indicated medicines inside the absence of contraindication in patients with vast life expectancy.[32,33]Inappropriate prescribing is common in older patients and is related to ADEs, hospitalization, and wasteful utilization of resources.[1] The major risk factors for potentially inappropriate prescribing (PIP) in older adults are advanced age, multiple comorbidities and polypharmacy.[34,35]PPI is often detected by using explicit (criterion based) and implicit prescribing indicators which aims to optimize prescription appropriateness and reduce negative outcomes.[36] Several guidelines are developed to help clinicians to enhance prescribing in older adults. TheScreening Tool for Older Persons Prescriptions (STOPP)and Screening Tool to Alert doctors to Right Treatment(START) are tools for identifying medications that willbe prescribed inappropriately and medications that willhave been omitted, respectively.[37,38,39]Implicit criteria are quality indicators of prescribing that a clinicianor a pharmacist can apply to any prescription. The Medication Appropriateness Indexes may be a well- known implicit tool. The systematic tool to reduce inappropriate prescribing (STRIP) incorporate both implicit and explicit prescribing indicators.[40]There is an association between potential inappropriate prescribing and harm for patients. By using these screening tools could also be an efficient way to avoid extra healthcare utilization, functional decline or reduced quality of life.[41]

INTERVENTIONS TO REDUCE DDI

Due to the presence of multiple diseases and complex therapeutic regimens in the patients, polypharmacy becomes unavoidable. Polypharmacy is an important cause of Drug-drug interactions (DDIs) which leads to the occurrence of Adverse Drug Reactions (ADRs).[42,43,44] DDIs are regularly predictable and subsequently preventable. In general, DDIs normally have a particular time course i.e. onset and duration. This makes DDIs more predictable and preventable than ADRs. So, one ought to be careful even as prescribing drugs which can cause delayed type of DDIs. The patients need to additionally be counselled for cautious monitoring of symptoms of ADR. Good documentation status gives proper knowledge and information about this and thus it can be preventable.[42] The clinical decision support system assists healthcare providers to identify the DDIs.[45,46] The laboratory testing of DDIs such as urine analysis has the potential to predict the DDIs.[45]

DEPRESCRIBING

Deprescribing is described as "the process of intentionally stopping or dose reduction of medicines in an individual to lessen medication burden and improve health outcomes".[46,47]Deprescribing decrease the risk of adverse events including medication-related hospital admissions and decreased cognitive function.[46,48] Appropriate deprescribing helps to reduce the drug-associated problems and economic remedy for seniors and public expenses.[49]

The barriers to deprescribing in clinical practice can be resolved by taking several steps. First, increased awareness in clinicians about deprescribing which helps them to withdraw inappropriate medication use in patients. Second, using of available medication or class-specific deprescribing tools. Third, the physicians must conduct a comprehensive review of the medications taken by the patient, particularly in geriatric patients. Due to presence of different health status in elder patient, discontinuation or reduced dose of medications can consider.[46]

NECESSITY OF RATIONAL DRUG THERAPY

Prescribing is the most evident tool used by the physicians to cure illness, to relieve the symptoms, to prevent future disease. Prescribing requires diagnostic skills, knowledge in common medicines and principles of clinical pharmacology, communication skills, and the ability to make decisions based on potential benefits and risks of the patient being treated. Rational prescribing describes the logical approach of making a differential diagnosis, estimating the prognosis, establishing the goals of therapy, selection of the most appropriate treatment monitoring the treatment effects.[50] For example the prescription rate of statins, antithrombotics, beta-blockers, and ACEI/ARB was found to be 7.8%, 5.1%, 3.3%, and 11%, respectively. The prescription rate of these drugs was found to be inappropriate in 36.2%, 22.4%, 64.5%, and 0%, respectively.[51] In treating coexisting conditions many commonly used medications need to be avoided whenever possible in patients with heart failure, based on known pharmacological principles and recommendations from guidelines.[52] Many antiarrhythmic drugs (class I agents) have cardio-depressant and pro arrhythmic effects. Non-dihydropyridine calcium channel blockers may adversely affect left ventricular function. Thiazolidinediones are not recommended in diabetic patients with advanced symptomatic heart failure because they cause fluid retention and exacerbates heart failure. Metformin is contraindicated in patients with heart failure who require drug treatment or with renal insufficiency, as this may lead to lactic acidosis.[52] Aspirin and clopidogrel alone or the combination of aspirin and clopidogrel were the commonly used antiplatelet drugs.[53] Coronary heart disease (CHD) is the largest contributor to CVD followed by Acute coronary syndromes (ACS) and acute myocardial infarction. Older patients tend to have multiple comorbidities and are hospitalized more often which increases the chances of polypharmacy and inappropriate prescribing. Polypharmacy was the most significant predictor of PIM use. [54] In older patients, there was a high incidence of PIM use associated along with the increased cost of the prescribed drugs.[55] A potentially inappropriate medication (PIM) is defined as a drug whose risk of an adverse event outweighs its clinical benefit.[54] The use of regular continuing medical education program by the hospital and educating and training doctors on rational prescribing will help alleviate this issue.[55] There are many drugs prescribed in a single patient to maximize efficacy in a particular condition. Prescribing rationally is important to minimize the chances of drug interactions, adverse drug reactions, and high cost of treatment. Evaluating the prescribing pattern and direct cost of therapy in patients admitted can also lead to the rationality of drugs.[53] The physicians and pharmacists should be aware of the ideal dosing of medications, the appropriate use of potentially life-saving drugs in patients with multiple comorbidity conditions and the treatment of coexisting illnesses.[52] Developing a multidisciplinary approach to evaluate and manage medications according to the complexities of an individual's medication regimen helps to reduce the risk of ADRs and the associated morbidity and mortality in a patient.[56]

DRUG UTILIZATION STUDY AN EFFECTIVE TOOL IN DRUG INTERACTIONS

Prescription writing is the transfer of therapeutic information from prescriber to the patient through the pharmacist.[57]There is an increase in average number of DDIs per patient as the number of drugs in the prescription increased.[58]The pattern of prescription is an investigational tool for prescribing, assessing, dispensing, and distribution of medicines.[59] Drug utilization study is an effective tool to determine the rationality of the prescription.[22] The Prescription should be analysed based upon the average number of drugs prescribed, drugs prescribed in generic names, and the total number of injections prescribed.[60] The analysis of prescription pattern helps to evaluate the current prescribing practice and to attend rational drug therapy.[61]The purpose of drug utilization studies is to estimate the proper drug therapy by analysing, identifying, and documenting the evidence-based medicine[62]. Drug utilization study consist of both diagnosis and lifestyle based information, that make it as a powerful scientific tool for rational and cost-effective usage of drugs in a society.[63]

IMPACT OF DRUG-DRUG INTERACTION TOWARDS QUALITY OF LIFE (QOL)

Drug-drug interactions (DDIs) are an emerging risk to the public health. They are significant but avoidable causes of morbidity and hospital admission that may present with harmful outcomes. Drug interaction is the modification of response of one drug by another when they are administered simultaneously or in quick succession.[64] The drug interaction mainlyoccurswhenever a patient concurrently receives more than one drug, and when thereis an increase in the number of drugs taken. Maintaining a good quality of life (QoL) is as important as survival to most patients living with a chronic, progressive illness. Individuals with heart failure have markedly impaired QoL compared to other chronic diseases. Patients with heart failure experience various symptoms such as dyspnea, fatigue, edema, sleeping difficulties, depression, and chest pain. These symptoms limit the patient's daily physical and social activities and thus results in poor QoL. Poor QoL is related to increase in hospitalization and mortality rates. Therefore, QoL in patients with heart failure should be assessed appropriately to determine its impact on patients daily lives.[65] COPD patients often have multiple comorbidities, such as diabetes mellitus and cardiac diseases, leading to polypharmacy. Drug-drug interactions (DDIs) may occur frequently and may cause serious adverse events and treatment failure.[66] Drug utilization research is important in clinical practice as it helps to facilitate the rational drug use. There is a need to bring changes in the prescribing practices particularly emphasizing on generic drug prescribing and restricting polypharmacy.[67] The use of a high number of drugs mainly parenteral drugs and intravenous fluids is a common problem. The prescription of generic drugs is low.[68] Polypharmacy was found to be the most important predisposing factor for ADRs. Most of the reactions were possible in causality, mild in severity, and not preventable. Intervention by clinical pharmacists might improve the reporting and monitoring aspects of ADRs.[69] Knowledge of the clinically important potential DDIs will help physicians and pharmacists identify patients that are at higher risk of DDI related adverse drug reactions.[64] Monitoring of prescription and drug utilization studies could identify the associated problems and provide feedback to the prescriber to create awareness about the irrational use of drugs.[70] Establishment of a system for the provision of medicines at a subsidized rate to patients might prove a useful step towards decreasing costs of health care burden. [67] The availability and affordability of good quality drugs along with their rational use are required for effective health care.[69] The Prescription audit is one important component of the clinical pharmacy, where clinical pharmacist plays an important role in the optimization of medication use, minimizing the number of medication-related problems and improving medication therapy.[71]Inappropriate use of drugs also leads to the increased cost of medical care, antimicrobial resistance, adverse effects, and patient mortality. Drug utilization studies focus on factors related to prescribing, dispensing, administering, and taking of medication and associated events.[72] DUR provides proper information to pharmacists for identifying prescription trends within different groups of patients whether he is in a disease state or in a drug-specific criterion. The purpose of DUR is to ensure drugs that the drugsused are appropriate, safe, and effective to improve the patient's health. DUR helps to prevent adverse drug reactions, toxicity, medication errors, drug-disease contraindications, drug-allergy interactions, drug-drug interactions, and therapeutic duplications.[72] Pharmacists can improve drug therapy for patients in collaboration with physicians and other members of the health care team.[71]

III. Conclusion

There seems to be a definite relationship between polypharmacy and drug-drug interactions. It is shown that elderly people with cardiac diseases are more prone to pDDI due their complicated therapy and comorbidity. Drug utilization study is being a solid investigational tool to reduce pDDI, increase rationality of prescription, reduce the incidence of ADRs, motivate deprescribing, reduce the hospital stay, increase positive health outcomes. DUS helps to educate physician about appropriate therapy, enhance the patient safety, efficacy and quality of life.

ABBREVIATIONS

DDIs :– Drug-Drug Interactions
ADRs :- Adverse Drug Reactions
ADE :- Adverse Drug Event
DUR :- Drug Utilization Review
pDDI :- Potential Drug-Drug Interactions
DUE :- Drug Utilization Evaluation
QoL :- Quality Of Life
COPD :- Chronic Obstructive Pulmonary Disease
CVD:- Cardiovascular Disease
CHD :- Congestive Heart Disease
ACS :- Acute Coronary Syndrome
HTN :- Hypertension
DM :- Diabetes Mellitus
PIP :- Potentially Inappropriate Prescribing
PIM :- Potentially Inappropriate Medication
STRIP :- The systematic tool to reduce inappropriate prescribing
STOPP :- Screening Tool for Older Persons Prescriptions
START:- Screening Tool to Alert doctors to Right Treatment
PADIs :- Potential Adverse Drug Interactions
CARD :- Causal Association Rule Discovery
MeSH :- Medical Subject Headings
EMA :- European Medicines Agency

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