The Professional Medical Journal
www.theprofesional.com

DOI: 10.17957/TPMJ/17.3670

REVIEW PROF-3670

1. Faculty of Pharmacy, Ziauddin University, Karachi, Pakistan
2. Associate Professor Faculty of Pharmacy, Jinnah Sindh Medical University, Karachi, Pakistan
3. Associate Professor, Faculty of Pharmacy, University of Karachi, Karachi, Pakistan
4. Dean and Professor, Faculty of Pharmacy, Ziauddin University, Karachi, Pakistan
5. Chairman Department of Medicine,Aga Khan Hospital, Dares salaam,Tanzania
6. Faculty of Pharmacy, Jinnah Sindh Medical University, Karachi, Pakistan
7.Associate Professor, Faculty of Pharmacy, Ziauddin University, Karachi, Pakistan
8. Faculty of Pharmacy, Ziauddin University, Karachi, Pakistan
9. Faculty of Pharmacy, Ziauddin University, Karachi, Pakistan

Correspondence Address:
Huma Ali
Associate Professor
Faculty of Pharmacy,
Jinnah Sindh Medical University,
Karachi, Pakistan.
humaali80@live.com

Article received on:
13/10/2016
Accepted for publication:
05/01/2017
Received after proof reading:
07/03/2017

DRUG-DRUG INTERACTION;

FACTS AND COMPARISONS WITH NATIONAL AND INTERNATIONAL BENTCH MARKS. A THREAT MORE THAN A CHALLENGE FOR PATIENT SAFETY IN CLINICAL AND ECONOMIC SCENARIO

Hina Hasnain[1], Huma Ali[2], Farya Zafar[3], Ali Akbar Sial[4], Kamran Hameed[5], Huma Shareef[6], Neelam Mallick[7], Anum Tariq[8], Rasheeda Fatima[9]

ABSTRACT… Drug-drug interaction (DDI) is a specific type of adverse event, which develops due to multiple regimen therapy, and that may lead to significant hospitalization and death. Clinical and economic impact of drug interactions are increasingly accredited as a chief concern in critical care. Potentiating effects of DDIs in intensive care units are far more critical due to complex medications regimen, high risk severely ill population and associated metabolic and physiological disturbances which can impede drug effects. Pharmacist contribution is classified as clarification of drug order, appropriate drug information provision, and advice for substitute treatment. A multidisciplinary approach is very necessary in developing a pharmaco-therapeutic regimen designed to optimize patient outcome and minimize any potential dug drug interactions. This review encompasses the prevalence, categorization, significance in term of patient safety and prescription efficacy, clinical and economic burdens, national and international data comparisons related to drug-drug interactions.

Key words: Drug-drug interactions, clinical and economic impact, significance, patient safety.

Article Citation: Hasnain H, Ali H, Zafar F, Akbar AS, Hameed K, Shareef H, Mallick N, Tariq A, Fatima R. Drug-drug interaction; facts and comparisons with national and international bentch marks; a threat more than a challenge for patient safety in clinical and economic scenario. Professional Med J 2017;24(3):357-365.
DOI: 10.17957/TPMJ/17.3670

INTRODUCTION

Drug- Drug Interactions (DDIs) is a phenomenon that occurs when one drug alters the effect of another drug given with it or during its span. Drug interactions may occur when one medicine modifies the pharmacokinetics of another drug or metabolites or may be reflected by the additive pharmacodynamic effects of either drug when taken concomitantly.[1-2] A drug effect may be potentiated, antagonized or otherwise changed by its specific interaction with other drugs, and such interactions can cause potentially harmful and unwanted responses, having severe side effects may ranging from treatment failure to severe adverse drug events.[3] Literature reveals that approx 10-17% of adverse drug events (ADE) are associated with DDIs in ICU subjects.[4] One of most frequently occurring reasons of Adverse drug reactions (ADRs) is drug interactions and it is more commonly seen in elderly patients due to poly-therapies that affects drug effectiveness[5-6] and it makes therapeutic drug management of patient more complicated.[7-8]

Several researchers have also investigated the frequency and characteristics of DDIs in a different hospital setting.[9-10] Potentiating effects of DDIs in an ICU are far more critical due to complex medications regimen, high risk severely ill population and associated metabolic and physiological disturbances which can impede drug effects.[11-12]

End organ damage, adverse drug events and prolong hospital stay are the results of the complications associated with DDIs. Evidence from epidemiologic studies suggest that drug interactions contribute to a small but significant number of adverse events in hospitalized patients and critically ill patients frequently receive complex multidrug regimen (Polypharmacy) with the goal of providing the superlative pharmaco-therapeutic support that can predispose them to these interactions.[13] Polypharmacy being

most common cause of initiation of DDIs since critically ill patients have been treated by health care professionals from variable specialties and hence wide range of drugs have been prescribed to the patients that has become major reason why patients who need intensive care are always more prone to develop several drug- drug interactions.[14]

There are many factors responsible for the development of risk and severity of DDIs such as number of drugs administered, duration of therapy, disease status and age of the patient. Certain diseases such as cirrhosis, renal failure and shock, along with poly medication, prolong periods of drug therapy and physiological aging changes are the main risk factors that can develop severe drug interactions.[9,15] Incidence and management data of DDIs in ICUs are still inadequate. In few studies, the higher percentages of DDIs in ICU patients were reported in the range of 45% to73% as well.[16-17]

Clinical Efficacy as well as prevalence of adverse drug reactions is directly proportional to the development of DDIs, the more drugs interact with each other, the more likelihood of adverse drug reactions and hence clinical effectiveness of medication will also be affected. In developed countries, there is probability of 20-40% of occurrence of DDIs in geriatric patients which is also one of the most common reason of medication error due to poly-pharmacy and the administration of various medication products to the elderly patients.[18-19]

HISTORIC BACKGROUND OF DDI

The initial reports on the interaction of the drug in the literature relating to the potential to increase or decreased drugs outcomes were not revealed until the year 1960s in which significantly prominent drug interactions reports along with more clinically relevant drug interaction data was started to unfold in the literature. Hypertensive crises were found in patients owing to the concurrent use of cheese and MAOIs which was the first case of clinically relevant drug interaction. Methods to detect DDIs were then systematically developed in, late 1960s proper prescription and dispensing practices progressed including drug interaction monographs. Further in the year 1970, drug manufacturing pharmaceutical companies were being asked by regulatory agencies to submit annual reports and comprehensive reviews in their national formulary systems on DDIs data.[20-21]

CLASSIFICATION OF DRUG-DRUG INTERACTIONS

It's highly important to classify drug–drug interactions for understanding the mechanisms and to have major insights into how to predict, detect, and avoid them.

The two main groups in which Drug-drug Interactions can be classified are as follows;

Pharmacokinetic

Involves absorption, distribution (protein binding, tissue binding), metabolism (hepatic, nonhepatic) and excretion (renal, nonrenal). Toxicities of medications and treatment failure are linked with pharmacokinetic interactions.

Pharmacodynamic

May be divided into three subgroups:

(1) Direct effect at receptor function.
(2) Interference with a biological or physiological control process.
(3) additive/opposed pharmacological effect.[22]

Several databases have been utilized to determine potential Drug Drug Interactions. The database of drugs.com has classified Drug-Drug Interactions into 3 groups; the first category is Major and all those drug combinations that results in clinically significant drug interactions have been classified as Major Drug Interactions since risks associated with these interactions overweighs the benefits associated. Furthermore, according to results showed by study of Sepehri et al, there is a prevalence of 10.8% associated with, major interactions[23] which further increases in the elderly patients[24], while Moderate interactions are less likely to produce any significant clinical consequences but they should be avoided and

the last category of minor drug interactions are associated with least likelihood to develop any clinically important drug interaction.[25] The relevance of drug-drug interactions as well as their importance can be very different, from minor to severe since many factors contribute in developing possible DDIs such as opportunistic infections, toxicity of drugs, immunological, clinical or virological failure as well as any new combination of drug.

PHARMACOKINETIC DRUG INTERACTIONS

The study of the time course of drug absorption, distribution, metabolism, and excretion has been defined as Pharmacokinetics. For safe as well as effective use of medications in individual patient, clinical pharmacokinetic plays a key role hence applications of the principals involved in pharmacokinetic of drugs for avoidance of such drug-drug interactions is necessary.[26] Pharmacokinetic interactions are often considered on the basis of knowledge of each drug and are identified by controlling the patient's clinical manifestations as well as the changes in serum drug concentrations.

Absorption

When the substances entered inside the body are up taken by the blood circulation, absorption takes place. There are several favorable factors which can promote drugs to interact each other such as drug absorption specificity for gastrointestinal tract that can lead to decreased or negligible bioavailability of drug.[27]

Distribution

For a drug to be efficacious, it is important for the drug to distribute in the body, the main proteins responsible for drug distribution and transportation are Albumin and alpha-1 glycoprotein. Drugs with high protein binding characteristic are more prone to develop drug interactions.[28]

Metabolism

Drug elimination is followed by metabolism of drug by a group of liver enzymes which can be induced or inhibited by drugs. The DDIs which show clinical relevance are generally occurring due to inhibition of liver enzymes by several drugs. According to the results of drug interaction study, it has been found that liver enzyme induction by a drug can even lead to serious complications.[29]

Excretion

Reabsorption, filtration, and secretion are main processes through which drug metabolites are eliminated from body and most of the drug interactions have been noticed at the stages of secretion and reabsorption.

PHARMACODYNAMIC DRUG INTERACTIONS

The type of DDIs that involves direct antagonism or addition of pharmacological effects of drugs and that occurs very close to target organ is Pharmacodynamics Interaction between different drugs. Moreover, owing to the negligible differences in the ranges of therapeutic index of many drugs, the pharmacodynamics reaction showed by such medications can be drastically variable which makes their process more complicated, raises chances of pharmacodynamic DDIs, hence such medication therapies must be rationalized.[30]

Main Compounds	Interacting Moiety	Possible Effect
Additive Interactions		
NSAIDs	SSRIs, Phenprocoumon	Increase risk of bleeding
NSAIDs	Glucocortocoids	Increase risk of bleeding
ACEIs	Spironolactone, amiloride	Hyperkalemia
SSRIs	Triptans	Serotonin Syndrome
TCAs	Low potency neuroleptics	Increase anticholinergic effects
Quonolones	Macrolides, citalopram	QT-Interval prolongation, torsade de points
Antagonistic Interactions		
Acetyl Salicylic Acid	Ibuprofen	Reduced effects
ACEIs	NSAIDs	Reduced effects
Levodopa	Classical Neuroleptics	Reduced effects
Phenprocoumon	Vitamin K	Reduced effects

Table-I. Examples of typical additive and antagonistic pharmacodynamic interaction[31]

SIGNIFICANCE OF DRUG INTERACTIONS

Drug interactions result in seriously harmful therapeutic outcomes such as potential adverse drug reactions and therapeutic failure of medication products therefore pharmacists must address such type of issues related to drug therapy and educating other teammates of health care setting. 6.7% of patients suffered from negative aspects of adverse drug reactions. Various influential factors which are jointly linked with the risk and severity of drug interactions are numbers of drugs prescribed and medication products administered treatment duration, patient age, stage of disease and number of prescribers. It is imperative to understand various mechanisms that have been involved in initiation of drug interactions along with their scientifically proven evidences in such an efficient and economic manner that can have a positive response on patient quality of life.[32]

FACTORS AFFECTING DRUG INTERACTIONS

There are various factors which need to be focused while assessing potentially important clinical consequences of DDIs. Narrow therapeutic index drugs, wide array of pharmacological activity of drug, metabolic enzyme induction or inhibition are few of many drug related factors that enhances the risk associated with DDIs that are clinically important while patient oriented factors are dietary habits and drug use, genetics of patient, age of patient, gender, concurrent disease states.[33]

ROLE OF HEALTHCARE PROVIDER IN DDIs IN COMPLEX CLINICAL SCENERIOS

Literature reveals that approx 10-17% of adverse drug events (ADE) are associated with DDIs in ICU subjects. Several researchers have also investigated the frequency and characteristics of DDIs in a different hospital setting.[9,11] Potentiating effects of DDIs in an ICU are far more critical due to complex medications regimen, high risk severely ill population and associated metabolic and physiological disturbances which can impede drug effects.[15-17] Many factors contribute in making ICU patients more prone to have serious interactions between drug therapies they have been administered due to their complexities in medication products, poor compliance, and severity of their disease state and organ failure.[34] According to a study which reveals that due to the contribution and participation of clinical pharmacists in medication therapy management of critically ill patients, statistically significant 66% of adverse drug reactions found to be minimized as well as it also enhances the use of medication among patients more effectively and safely.[35] Clinical pharmacists are crucial members of health care team since their knowledge regarding drug therapy plays major role even at the time of discharge of patient while educating and counsel the patients regarding their prescription medication as per the results of one study on older adult population of patients.[36] Due to the provision of evidence based clinical knowledge to every member of heath care team, clinical pharmacists considered to be most responsible providers of critical care, education, research based knowledge and management services for the patient's health.

DRUG INTERACTION FACTS IN UNDERDEVELOPED NATIONS

One of the numerous reasons of patient's deteriorating health conditions and therapeutic failures is co-prescriptions of interacting medications that not only put patients in danger but further complicate patient health status especially in rudimentary health care setting specifically in clinical setting of countries such as Pakistan, India, Bangladesh and other developing nations around the globe etc.[37] According to one study, Pakistan has been facing many health related issues including reasons due to DDIs and their clinical consequences which range from 45 to 77.5%. The prevalence of Drug interaction per patient was found to 1.44 per patient in Ethiopia. Similar results have been revealed in Bangladesh where due to very poor drug information facilities in health care settings, accompanying the scarcity of lot of clinical data and drug information provided by drug labeling services as well as lack of research in drug science results in potential drug interaction and compromise patient safety.[38] In Nigeria, at least two interacting drugs were prescribed to patient in tertiary care

health settings and 55.6% was found to be the prevalence of DDIs.[39] Similar study executed in Palestinian patients revealed more than half drug interactions in patients. According to a study conducted in India, incidence rates of 30.7% were found in patients, likewise 21.3% was recorded in Nepal.

BENCHMARKS OF DRUG INTERACTIONS IN DEVELOPED NATIONS

Prevalence of drug interactions in developed countries is comparatively high due the effective drug monitoring system implementation and pharmacovigilance setup. Few of the significant figures have been reported by one research investigation conducted in 2004 in Italy, have shown that 6.0% of Italian population who was indulged in the study, have been prescribed drugs potentially interacting with one another as well as patients got most commonly available medications having incidence rates of 13.2% to interact with co-prescribed drug product. Another Brazilian study conducted at different time courses in hospitalized patients study suggested prevalence of drug interaction among simultaneously prescribed medication up to 70%. Moreover prevalence of patients with interactions was between 15 and 45 % and the number of interactions per 100 patients was between 37 and 106, depending on the group of studies analyzed in Italy. From 5,336 prescriptions given to patients in Brazil with two or more drugs, 3,097 (58.0%) contained potential drug interactions (pDDI). The frequency of major and well document pDDI was 26.5%. Among 647 patients, 432 (66.8%) were exposed to at least one pDDI and 283 (43.7%) to major Pddi.[40-41]

COMPARISION AND FACTS

From above mentioned figures regarding prevalence of DDIs among different sets of population in diversely distributed areas worldwide, it can be sum upped that rates for occurrence of these interactions is with contradictory values in developed countries, or under- recognized especially in case of developing corners of the world. Significant proportion of drug interaction studies data is still lacking. weakened human resource indicators such as health and nutrition, education and literacy among young and older adults, widespread utilization of substandard and illicit drug products, unawareness about pharmacotherapy and patient responses to health practitioners, time constraints, increased percentage of trafficking in drug precursors and enhanced use of tobacco smoking are very few of various factors responsible of these pitfalls in drug therapy management of patients. This health issue can be predicted, prevented and managed by researching on science of drug metabolism and being responsible in drug therapy decision making to achieve good health outcomes.

ECONOMIC BURDEN/IMPACT OF DRUG INTERACTIONS

Drug interactions have become a major reason of adverse drug events and the cot associated with these adverse drug reactions inspected up to $177.4 billion rupees. Several studies have been demonstrates the importance and link of cost- effective therapy to patients and potential Drug Interactions that further increase chances to enhance financial burden on patients therefore health care practitioners ought to look upon rationale prescribing to their patients in such a way that major DDIs must be avoided. Cost saving can be achieved if the drug therapy is managed in a way that treatment of patients must be rationalized to raise cost effective pharmacotherapy. According to results of a study conducted in India, when there was minimal polypharmacy in patients treated, savings of 17 US $ per patient was achieved and the GNP (Gross National Product) was found to be more than 5% per capita. One of the major reasons of adverse drug interactions from improper utilization of medication is DDIs as well as polypharmacy, off-label use of drugs along with inconsequential use of medical products that ultimately results in further clinical and economic complications in patients. As per results revealed through a study conducted for a duration of six months in an in-patient setting, it was found that the patients who had experienced any DDIs were prone to hospitalize more with prolongation in hospital stays, Moreover patients with DDIs were associated with more utilization

of hospital services and recourses along with elevated treatment cost and financial burden as compare to patients who did not have any drug interaction.[42-43]

RECOMMENDATIONS TO REDUCE DDI

Choosing suitable alternatives in the case of major potential DDIs and closer patient monitoring in the case of moderately occurring DDIs, are ways in which physicians can minimize the risk or prevent AEs. It is the responsibility of health care professionals to weigh risk versus benefit when prescribing and dispensing. According to the results revealed from a cohort study. 13.3% of medication related errors that can be prevented and involves those prescriptions of drugs that are quite known for interactions results in adverse drugs events. Moreover, approximately 75% of patient admissions in hospital owing to medication related issues have found to be preventable as per study report in Australia. It is compulsory to keep patient prescription as simple as possible that can be easily reexamined periodically by health care providers. Developing drug interaction information systems and by interweaving computer-aided drug interaction screening software's is imperative and a way forward in combating with the complications of drug interactions in clinically sensitive patients. Bar coding systems as well as electronic prescribing patterns such as computerized physician orders are now recognized as more substantial means to minimize DDIs chances and have countless advantages.[44-45]

Furthermore it is important to educate treating physicians regarding DDIs that can provide them an insight into drug utilization review and promote rational prescribing patterns for patient individualized therapy. Medication management tools such as ARMOR may also b utilized by practitioners for better patient outcome of treatment.[46] By appropriate blending of health policies and regulatory measures having major focus on withdrawal of harmful medication products, controlled substance use and abuse, following evidence based treatment options as well as approving more safer drug generic and alternatives can also serves to be step to prevent these drug interactions.[47] One more strategy to avoid and minimize the incidence of drug interactions is to promote Pharmacovigilance as a crucial part of post marketing surveillance of drug products so that all medications administered to patients undergo strict check with timely detection and assessment of any dug related problem.

CONCLUSION

Drug interactions are one of the major causes of adverse drug reactions, therapeutic failure and high economic treatment outcomes. Therefore clinical pharmacist must ensure that the combination therapy of interacting drugs must be avoided in patients and promote the selection of non- interacting alternative for the drug either for the object drug or the precipitant drug or both. Pharmacist provide an in depth knowledge regarding dose, frequency and route of administration of the drug as well as monitor laboratory findings which correlates with the administered drugs. Moreover, the Clinical Pharmacist also provides education regarding the risk factors associated with the development of drug interactions which can further deteriorate patient drug therapy and medical condition.

REFERENCE

1. Stockley IH, editor. **2002 Stockley's Drug Interactions, 6 (edn).** London: Pharmaceutical Press.

2. Mouly S, Meune C, Bergmann JF. Mini□series: I. **Basic science. Uncertainty and inaccuracy of predicting CYP□mediated in vivo drug interactions in the ICU from in vitro models: focus on CYP3A4 Intensive Care Med.** 2009; 35:417–29.

3. Krahenbuhl MA, Schlienger R, Lampert M, Haschke M, Drewe J, Krahenbuhl S. **Drug-related problems in hospitals: a review of the recent literature.** Drug Saf 2007; 30:379–407.

4. Reis AMM, de Bortoli CCH. **Adverse drug events in an intensive care unit of a university hospital.** Eur J Clin Pharmacol 2011; 67:625–32.

5. Gallelli L, Colosimo M, Pirritano D, Ferraro M, De Fazio S, Marigliano NM, et al. **Retrospective evaluation of adverse drug reactions induced by nonsteroidal anti-inflammatory drugs.** Clin Drug Investig.2007; 27:115–22.

6. Gallelli L, Colosimo M, Tolotta GA, Falcone D, Luberto L, Curto LS, et al. **Prospective randomized double-blind trial of racecadotril compared with loperamide in elderly people with gastroenteritis living in nursing homes.** Eur J Clin Pharmacol. 2010; 66:137–44.

7. Siniscalchi A, Gallelli L, Avenoso T, Squillace A, De Sarro G. **Effects of carbamazepine/oxycodone coadministration in the treatment of trigeminal neuralgia.** Ann Pharmacother. 2011; 45:e33.

8. Canu B, Fioravanti A, Orlandi P, Di Desidero T, Alì G, Fontanini G, et al. **Irinotecan synergistically enhances the antiproliferative and proapoptotic effects of axitinib in vitro and improves its anticancer activity in vivo.** Neoplasia. 2011; 13:217–29.

9. Zwart V, Rijkom JE, Uijtendaal EV, ten Berg MJ, van Solinge WW, Egberts ACG. **Frequency and nature of drug-drug interactions in a Dutch university hospital.** Br J Clin Pharmacol 2009; 68:187–93.

10. Reimche L, Forster AJ, van Walraven C. **Incidence and contributors to potential drug-drug interactions in hospitalized patients.** J Clin Pharmacol 2011; 51:1043–50.

11. Zagli G, Tarantini F, Bonizzoli M, Di Filippo A, Peris A, De Gaudio AR, et al. **Altered pharmacology in the intensive care unit patient.** Fundam Clin Pharmacol. 2008; 22:493–50. 10.1111/j.1472□8206.2008.00623.x.

12. Spriet I, Meersseman W, de Hoon J, et al. Mini-series: II. **Clinical aspects: clinically relevant CYPP450-mediated drug interactions in the ICU.** Intensive Care Med 2009; 35:603–12.

13. Lima REF, Cassiani SHB. **Potential drug interactions in intensive care patients at a teaching hospital.** Rev Lat Am Enfermagem 2009; 17:222–7.

14. Tari L, Anwar S, Liang S, Cai J, Baral C. **Discovering drug-drug interactions: a text-mining and reasoning approach based on properties of drug metabolism.** Bioinformatics. 2010; 26:547–53.

15. Mohamed H, Mudalipalayam NS, and Ganesh V. **Impact of clinical pharmacist in an Indian Intensive Care Unit, J Crit Care Med.** 2016 Feb; 20(2): 78–83.

16. Cruciol SJM, Thomson JC. **Prevalence of potential drug□drug interactions and its associated factors in a Brazilian teaching hospital.** J Pharm Pharm Sci. 2006; 9:427–33.

17. Smithburger PL, Kane-Gill SL, Seybert AL. **Drug-drug interactions in cardiac and cardiothoracic intensive care units.** Drug Saf 2010; 33:879–88.

18. Smithburger PL, Kane-Gill SL, Seybert AL. **Drug-drug interactions in the medical intensive care unit: an assessment of frequency, severity and the medications involved.** Int J Pharm Pract 2012; 20:402–8.

19. Caterina P, Antonello DP, Chiara G, Chiara C, Giacomo L, Antonio S, Giovambattista DS, and Luca G. **Pharmacokinetic drug-drug interaction and their implication in clinical management, J Res Med Sci.** 2013 Jul; 18(7): 601–610.

20. Blackwell B. **Hypertensive crisis due to monoamine-oxidase inhibitors.** Lancet. 1963 Oct 26; 2(7313):849-50.

21. Sjöqvist F, Böttiger Y. **Historical perspectives: drug interactions - it all began with cheese.** J Intern Med. 2010 Dec; 268(6):512-5.

22. J K Aronson, **Classifying drug interactions, Br J Clin Pharmacol.** 2004 Oct; 58(4): 343–344.

23. Sepehri G, Khazaelli P, Dahooie FA, Sepehri E, Dehghani MR. **Prevalence of potential drug interactions in an Iranian general hospital.** Indian J Pharm Sci. 2012; 74(1):75–79.

24. Obreli Neto PR, Nobili A, Marusic S, Pilger D, Guidoni CM, Baldoni Ade O, Cruciol-Souza JM, Da Cruz AN, Gaeti WP, Cuman RK. **Prevalence and predictors of potential drug-drug interactions in the elderly: a cross-sectional study in the brazilian primary public health system.** J Pharm Pharm Sci. 2012; 15(2):344–354.

25. Tracia-Gay Kennedy-Dixon, Maxine Gossell-Williams, Jannel Hall, and Blossom Anglin-Brown, **The prevalence of major potential drug-drug interactions at a University health centre pharmacy in Jamaica.** Pharm Pract (Granada). 2015 Oct-Dec; 13(4): 601.

26. Mantia G, Provenzano G. **Rilevanza clinica delle interazioni farmacologiche di tipo farmacocinetico.** Acta Medica Mediterr. 2008; 24:23–27.

27. Krishna G, Moton A, Ma L, Medlock MM, McLeod J. **Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers.** Antimicrob Agents Chemother. 2009; 53:958–66.

28. Ogawa R, Echizen H. **Clinically significant drug interactions with antacids: An update.** Drugs.2011; 71:1839–64.

29. Seedher N, Agarwal P. **Effect of metal ions on some pharmacologically relevant interactions involving fluoroquinolone antibiotics.** Drug Metabol Drug

Interact. 2010; 25:17–24.

30. Tamargo J, Le Heuzey J-Y, Mabo P. **Narrow therapeutic index drugs: a clinical pharmacological consideration to flecainide.** European Journal of Clinical Pharmacology. 2015; 71(5):549-567.

31. Cascorbi I. Drug Interactions—Principles, **Examples and Clinical Consequences.** Deutsches Ärzteblatt International. 2012; 109(33-34):546-556.

32. Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, et al. **Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: The randomized, double.** Blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol. 2008; 51:256–60.

33. Gallelli L, Gioffrè V, Vero G, Gallelli A, Roccia F, Naty S, et al. **Clarithromycin in the Treatment of Legionella pneumophila Pneumonia Associated with Multiorgan Failure in a Previously Healthy Patient.** Clin Drug Investig. 2005; 25:485–90.

34. Ismail M, Iqbal Z, Khattak MB, Javaid A, Khan TM. **Prevalence, type and predictors of potential drug-drug interactions in pulmonary ward of a tertiary care hospital.** Afr J Pharm Pharmacol 2011; 5:1303-9.

35. Ismail M, Iqbal Z, Khattak MB, Khan MI, Arsalan H, Javaid A, et al. **Potential drug-drug interactions in internal medicine wards in hospital setting in Pakistan.** Int J Clin Pharm 2013; 35:455-62.

36. Ismail M, Iqbal Z, Khattak MB, Javaid A, Khan TM. **Potential drug-drug interactions in cardiology ward of teaching hospital.** Health Med 2012; 6:1618-24.

37. Soherwardi S, Chogtu B, Fizal P. **Surveillance of the potential drug-drug interactions in medicine department of a tertiary care hospital.** J Clin Diagn Res 2012; 6:1258-61.

38. Bhagavathula AS, Berhanie A, Tigstu H, Yishak A, Getachew Y, Khan TM, et al. **Prevalence of potential drug-drug interactions among internal medicine ward in University of Gondar teaching hospital, Ethiopia.** Asian Pac J Trop Biomed 2014; 4 Suppl 1:S204-8.

39. Fadare JO, Ajayi AE, Adeoti AO, Desalu OO, Obimakinde AM, Agboola SM. **Potential drug-drug interactions among elderly patients on anti-hypertensive medications in two tertiary healthcare facilities in Ekiti State, South-West Nigeria.** Sahel Med J 2016; 19:32-7.

40. Daniela ODM, Eliane R, Sílvia S. **Potential drug-drug interactions in a Brazilian teaching hospital: age-related differences? Rev Ciênc Farm Básica Apl.** 2015;36(3):435-444 ISSN 1808-4532.

41. Tragni E, Casula M, Pieri V, et al. **Prevalence of the Prescription of Potentially Interacting Drugs.** Alessi-Severini S, ed. PLoS ONE. 2013; 8(10):e78827.

42. Robert Taylor Jr, Joseph V Pergolizzi Jr, R Amy Puenpatom, and Kent H. **Economic implications of potential drug–drug interactions in chronic pain patients, SummersExpert Review Of Pharmacoeconomics & Outcomes Research Vol.** 13 , Iss. 6,2013.

43. Sultana J, Cutroneo P, Trifirò G. **Clinical and economic burden of adverse drug reactions. Journal of Pharmacology & Pharmacotherapeutics.** 2013; 4(Suppl1):S73-S77.

44. Bates DW, Leape LL, Cullen DJ, Laird N, Petersen LA, Teich JM et al. **Effect of computerized physician order entry and a team intervention on prevention of serious medication errors.** JAMA 1998; 280(15):1311–1316.

45. Salwe KJ, Kalyansundaram D, Bahurupi Y. A Study on Polypharmacy and Potential Drug-Drug Interactions among Elderly Patients Admitted in Department of Medicine of a Tertiary Care Hospital in Puducherry. Journal of Clinical and Diagnostic Research : JCDR. 2016; 10(2):FC06-FC10.

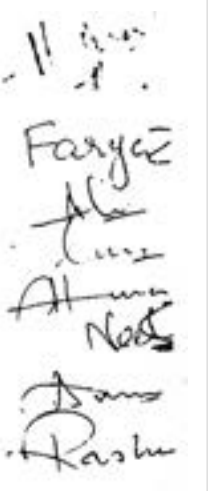
46. Haque R. **ARMOR: a tool to evaluate polypharmacy in elderly persons.** Ann Long-Term Care. 2009; 17(6):26-30.

47. Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. **Polypharmacy: Misleading, but manageable.** Clinical Interventions in Aging. 2008; 3(2):383–89.

"A bad attitude is like a flat tire,
you can't get very far until you change it."

Unknown

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Hina Hasnain	Equal contribution of all authors	
2	Huma Ali		
3	Farya Zafar		
4	Ali Akbar Sial		
5	Kamran Hameed		
6	Huma Shareef		
7	Neelam Mallick		
8	Anum Tariq		
9	Rasheeda Fatima		