IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON MECHANISM , MANAGEMENT AND FUTURE PROSPECTS FOR THE DRUG DRUG INTERACTION

Vaibhav Haramkar* , Shrikrushna Subhash unhale , Baliram Bhutekar , Sujata Salve , Vaishnavi Patil , prof Pavan Folane , Prof . Dr. K .R. Biyani

Anuradha college of pharmacy , chikhli , Dist –Buldana (MS) India 443201

ABSTRACTS :

In the future , many drug- drug interactions (DDI) scenarios may be mapped using computer simulations but for now , laboratories are working to keep up with ever – shifting regulations including those for in vitro metabolism and transporter mediate DDI studies .

A change in a drugs effect on the body when the drug is taken together with a second drug . A DDI can delay decrease or enhance absorption of either drug .this can decrease or increase the action of either or both drugs or cause adverse effects.

One example of this type of DDI is where the therapeutic protein changes the level of cytochrome P450 (cyp enzyme) . In the liver , where this Change In the cyp enzyme has an effect on the coadministered small molecule drug .

Key words : DDI – drug drug interactions , Drugs , absorption , adverse effects , Cytochrome P450 , enzymes

INTRODUCTION :

The topic of drug–drug interactions (DDIs) has received a great deal of recent attention from the regulatory, scientific, and health care communities worldwide. A large number of drugs are introduced every year, and new interactions between medications are increasingly reported. Consequently, it is no longer practical for physicians to rely on memory alone to avoid potential drug interactions. Precipitant drugs modify the object drug's absorption, distribution, metabolism, excretion, or actual clinical effect.

A drug interaction is a change in the action or side effects of a drug caused by concomitant administration with a food, beverage, supplement, or another drug. There are many causes of drug interactions. For example, one drug may alter the pharmacokinetics of another. Alternatively, drug interactions may result from competition for a single receptor or signaling pathway. The risk of a drug-drug interaction increases with the number of drugs used. Over a third (36%) of the elderly in the U.S. regularly use five or more medications or supplements, and 15% are at risk of a significant drug-drug interaction.

A drug-drug interaction may increase or decrease the effects of one or both drugs. Clinically significant interactions are often predictable and usually undesired . Adverse effects or therapeutic failure may result. Rarely, clinicians can use predictable drug-drug interactions to produce a desired therapeutic effect. For example, coadministration of lopinavir and ritonavir to patients with HIV infection results in altered metabolism of lopinavir and increases serum lopinavir concentrations and effectiveness.
Drug interactions involve

- Pharmacodynamics
- Pharmacokinetics

In **pharmacodynamic interactions,** one drug alters the sensitivity or responsiveness of tissues to another drug by having the same (agonistic) or a blocking (antagonistic) effect. These effects usually occur at the receptor level but may occur intracellularly.
In **pharmacokinetic interactions,** a drug usually alters absorption, distribution, protein binding, metabolism, or excretion of another drug. Thus, the amount and persistence of available drug at receptor sites change. Pharmacokinetic interactions alter magnitude and duration, not type, of effect. They are often predicted based on knowledge of the individual drugs or detected by monitoring drug concentrations or clinical signs.

MECHANISM OF DRUG INTERACTIONS

Drug interactions can be broadly divided into pharmacokinetic and pharmacodynamic interactions.In certain cases, however, the mechanisms are complex and may not be well understood. Few interactions take place even outside the body when drug solutions are mixed before administration.

Pharmacokinetic interactions

These interactions alter the concentration of the object drug at its site of action (and consequently the intensity of response) by affecting its absorption, distribution, metabolism or excretion.

- Alteration of absorption or first-pass meta-
bolism
- Displacement of plasma protein bound drug
- Alteration of drug binding to tissues affecting
volume of distribution and clearance
- Inhibition/induction of metabolism
- Alteration of excretion

Absorption

Absorption of an orally administered drug can be affected by other concurrently ingested drugs. This is mostly due to formation of insoluble and poorly absorbed complexes in the gut lumen, as occurs between tetracyclines and calcium/iron salts, antacids or sucralfate. Phenytoin absorption is decreased by sucralfate due to binding in the g.i. lumen. Such interactions can be minimized by adminstering the two drugs with a gap of 2–3 hours so that they do not come in contact with each other in the g.i.t. Ketoconazole absorption is reduced by H2 blockers and proton pump inhibitors because they reduce gastric acidity which promotes dissolution and absorption of ketoconazole. Antibiotics like ampicillin, tetracyclines, cotrimoxazole markedly reduce gut flora that normally deconjugates oral contraceptive steroids secreted in the bile as glucuronides and permits their enterohepatic circulation. SeveralSeveral instances of contraceptive failure have been reported with concurrent use of these antibiotics due to lowering of the contraceptive blood levels. Alteration of gut motility by atropinic
drugs, tricyclic antidepressants, opioids and prokinetic drugs like metoclopramide or cisapride can also affect drug absorption.

Distribution

Interactions involving drug distribution are primarily due to displacement of one drug from its binding sites on plasma proteins by another drug. Drugs highly bound to plasma proteins that have a relatively small volume of distribution like oral anticoagulants, sulfonylureas, certain NSAIDs and antiepileptics are
particularly liable to displacement interactions. Another requirement is that the displacing drug should bind to the same sites on the plasma proteins with higher affinity. Displacement of bound drug will initially raise the concentration of the free and active form of the drug in plasma that may result in toxicity. However, such effects are usually brief, because the free form rapidly gets distributed, metabolized and excreted, so that steady-state levels are only marginally elevated. The clinical outcome of displacement interactions is generally significant only when displacement extends to tissue binding sites as well, or is accompanied by inhibition of metabolism and/ or excretion. Quinidine has been shown to reduce the binding of digoxin to tissue proteins as well as

its renal and biliary clearance by inhibing the efflux transporter P-glycoprotein, resulting in nearly doubling of digoxin blood levels and toxicity.

Metabolism

Certain drugs reduce or enhance the rate of metabolism of other drugs. They may thus affect the bioavailability (if the drug undergoes extensive first pass metabolism in liver) and the plasma half-life of the drug (if the drug is primarily eliminated by metabolism). Inhibition of drug metabolism may be due to competition for the same CYP450 isoenzyme or cofactor, and attains clinical significance mostly for drugs that are metabolized by saturation kinetics. Macrolide antibiotics, azole antifungals, chloramphenicol, omeprazole, SSRIs, HIV-protease inhibitors, cimetidine, ciprofloxacin and metronidazole are some important inhibitors of metabolism of multiple drugs. Risk of statin induced myopathy is increased by fibrates, niacin, erythromycin, azole antifungals and HIV-protease inhibitors,

probably due to inhibition of statin metabolism.Because lidocaine metabolism is dependent on hepatic blood flow, propranolol has been found to prolong its t½ by reducing blood flow to the liver.A number of drugs induce microsomal drug metabolizing enzymes and enhance biotransformation of several drugs (including their own in many cases). Induction involves gene mediated increased synthesis of certain CYP450 is ; takes 1–2 weeks of medication with the inducer to produce maximal effect (contrast inhibition of metabolism which develops quickly) and regresses gradually over 1–3 weeks after discontinuation of the inducer. Barbiturates, phenytoin, carbamazepine, rifampin, cigarette

smoking, chronic alcoholism and certain pollutants are important microsomal enzyme inducers. Instances of failure of antimicrobial therapy with metronidazole, doxycycline or chloramphenicol have occurred in patients who are on long-term medication with an inducing drug. Contraceptive failure and loss of therapeutic effect of many other drugs have occurred due to enzyme induction. On the other hand, the toxic dose of paracetamol is lower in chronic alcoholics and in those on enzyme inducing medication, because one of the metabolites of paracetamol is responsible for its overdose hepatotoxicity.

Excretion

Interaction involving excretion are important mostly in case of drugs actively secreted by tubular transport mechanisms, e.g. probenecid inhibits tubular secretion of penicillins and cephalosporins and prolongs their plasma t½. ThisThis is particularly utilized in the single dose treatment of gonorrhoea. Aspirin blocks the uricosuric action of probenecid and decreases tubular secretion of methotrexate. Change in the pH of urine can also affect excretion of weakly acidic or weakly basic drugs. Thus has been

utilized in the treatment of poisonings. Diuretics and to some extent tetracyclines, ACE inhibitors and certain NSAIDs have been found to raise steady-state blood levels of lithium by promoting its tubular reabsorption.

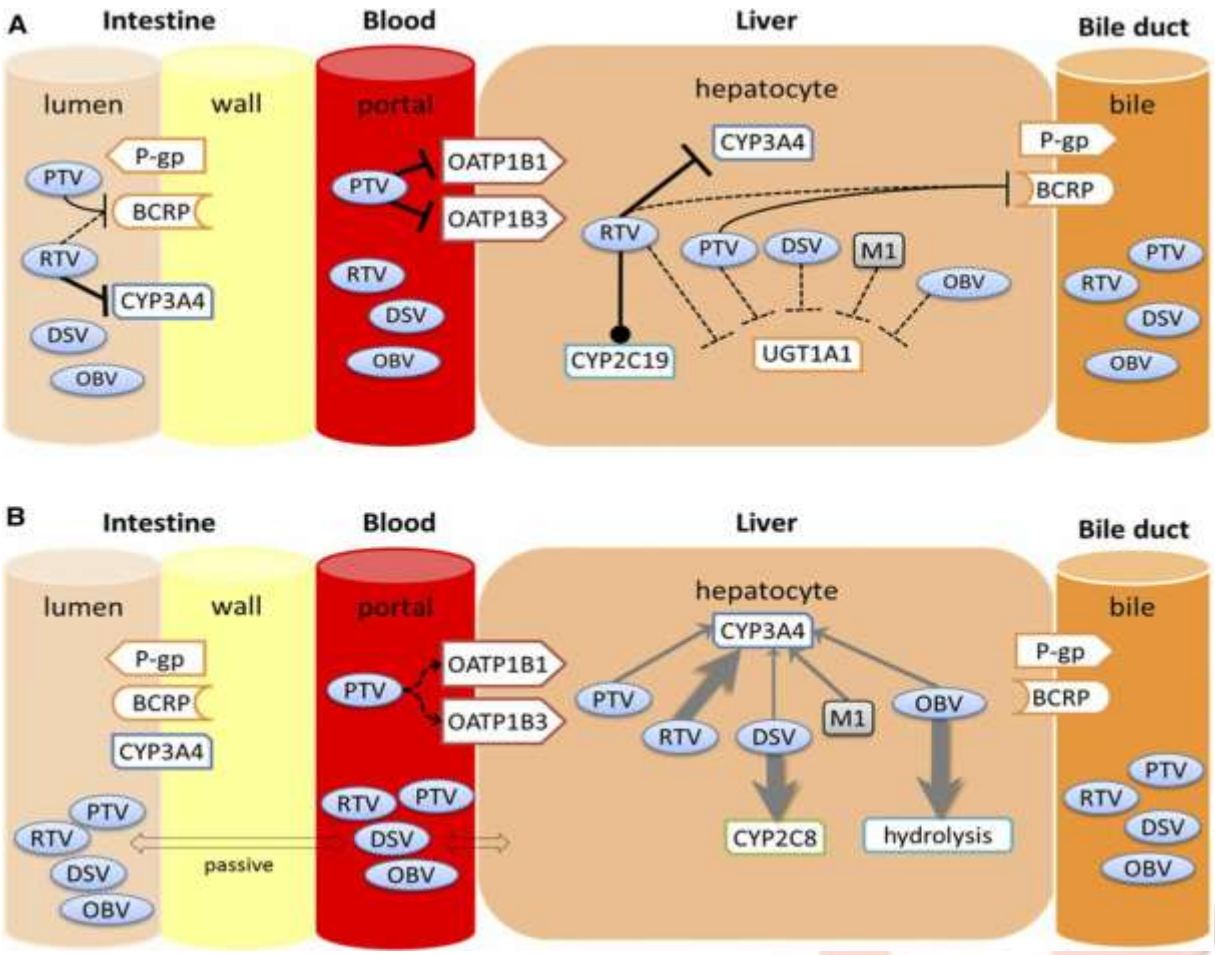

Fig. Mechanisms of Drug Drug Interaction

Pharmacodynamics interactions

These interactions derive from modification of the action of one drug at the target site by another drug, independent of a change in its concentration. This may result in an enhanced response (synergism), an attenuated response (antagonism) or an abnormal response. they are deliberately utilized in therapeutics for various purposes. Of clinical significance are the in-advertent concurrent administration of synergistic or antagonistic pair of drugs with adverse consequences. Some examples are:

1. Blunting of K+ conserving action of spironolactone by aspirin, because it inhibits the tubular secretion of canrenone (an active metabolite of spironolactone).

2. Blockade of antiparkinsonian action of levodopa by neuroleptics and metoclopramide having antidopaminergic action.

Future prospects for drug drug Interaction

Expanding the Scientific Knowledge Base

Although progress has been made in understanding the aging process, there is still a paucity of data at the intracellular, organ, system, and population levels. The impact of aging on cells and organ systems has commonly been studied in isolation; however, a more integrated approach is needed that will examine the effects of aging on the body. Pharmacokinetic and pharmacodynamic models need to be developed that encompass the entire range of changes occurring at multiple levels throughout the body.

The following list highlights specific areas of research that would add to the body of knowledge and clarify our understanding of the aging process especially with regard to improving pharmacotherapy. This list is by no means comprehensive, as numerous research avenues could yield important information on the impact of pharmacotherapy and drug interactions in the elderly. Areas for future research include the impact of aging, gender, genetics, and ethnicity on physiology and metabolic processes. Specifically,

1. Age related changes in cellular transport mechanisms and extrahepatic metabolism and transport including the activity of different enzyme isoforms;
2. biomarkers of drug exposure;
3. mechanisms that cause variable responses to medications in aging racial and ethnic populations;
4. age-related hormonal changes affecting drug metabolism or drug sensitivity;
5. the impact of nutrition on the aging process;
6. mechanisms underlying diseases prevalent in the elderly (e.g., hypertension, diabetes, osteoporosis, and Parkinson's and Alzheimer's disease);
7. in vitro models for multiple drug regimens and multiple drug interactions that may be predictive of and correlated with in vivo research;
8. models for drug interaction related to altered reflex activity and changing homeostatic mechanisms;
9. the potential beneficial and adverse health effects of nutraceuticals; and
10. social and psychological aspects of medication use in the elderly (e.g., access to medications, adherence to prescription regimens), with a special emphasis on minority populations.

Much about biologics

The drug development pipeline includes many biologics and therapeutic proteins. But when it comes to DDI studies, “anything that’s not a small molecule has the potential to be challenging,” warns Butler. Adds Laethem, “the models we have are not really adequate for addressing questions” raised by non-small molecule drugs. The FDA’s 2012 guidance briefly mentions therapeutic proteins, but the 2017 guidance clearly addresses only small molecule DDI studies, leaving industry unsure of how to proceed. “It’s not clear what needs to be done,” admits Reinen. “Most often, the proteins are really well soluble, so it’s not an issue. We use the same approach we use for pharmaceuticals.” Generally, experts agree that small molecules have the highest DDI risk,

so it hasn't been quite as urgent to map the DDI risk of biologics, observes Bush. "Most of these proteins and peptides don't interact with cytochrome P450 in the same way," he explains. Nonetheless, he recommends a degree of caution: "Just because you're working with a protein or peptide doesn't mean you're 100% off the hook with drug interactions."

There could be downstream synergistic effects that create adverse events. For example, says Bush, the glucagon-like peptide-1 class of diabetes drugs can cause delayed gastric emptying, which might, in turn, affect the absorption of other oral medications. "Our standard approach with small molecules," Butler remarks, "doesn't necessarily fit outside of that space."

Although companies are trying to keep up by developing new systems, the DDI studies for non-small molecule drug candidates are, in Laethem's estimation, more experimental. "While some companies are willing to try these things out, I think one of the biggest drivers is going to be a blessing from the FDA," he emphasizes. That blessing may soon come, with the FDA announcing last year that it would be taking comments and suggestions on the best way to evaluate DDI studies for therapeutic proteins.

Today, more than 20% of adults take three or more prescription drugs, according to the Centers for Disease Control and Prevention. As the number of people taking more than one drug continues to increase, so too will the risk of drug interactions. Soon, many DDI scenarios could be mapped using computer simulations, but for now, laboratories across the globe are working to keep up with ever-shifting regulations for DDI laboratory studies.

Research Methodologies and Tools

Trials of acute drug use are well funded; however, there are few long-term studies that examine chronic effects and drug interactions. Inasmuch as elderly persons are living longer and may take the same medications for many years, increased postmarketing surveillance is needed to examine the effects of long-term use of drugs. Incentives to strengthen postmarketing surveillance should be considered. Some of these drugs (e.g., hormone replacement therapy, antidepressants, and lipid-lowering medications) may be used as preventive measures (e.g., treating high cholesterol levels in the absence of cardiovascular disease or prescribing hormone replacement therapy to prevent hip fractures); however, their long-term health effects are not fully known. Further, the pharmacodynamics of many of these medications are only beginning to be investigated.

Future prospects of drug information center

Although DICs have existed since the 1960s, their full potential has not been explored, especially in developing countries. Although future growth in the number of centers will be limited, their present activities will become more refined and productive if the above-mentioned challenges are appropriately addressed.DICs can also provide information about complementary and alternative medicines, which would especially be beneficial in developing countries where a large number of patients consume these medicines. In India, DICs within academic centers can collaborate with the existing in-house department of complementary and alternative medicines (AUYSH) to provide such information.Novel initiatives such as providing TDM service, adverse drug monitoring and

collaboration with forensic scientists for identification of illicit substances, forensic pharmacology, postmortem toxicology, and providing expert testimony have been successfully tried in Denmark and can be replicated in India too. Other activities such as online or offline academic detailing where specially trained pharmacists/pharmacologists with detailed medication knowledge interact with physicians to share the best practices of prescribing have been described as a means of promoting evidence-based medicine practices and rational use of drugs. Such activities may also yield positive results if tried in Indian setting

Risk factors of DDI

Risk factor	Potential result
Acute medical condition (eg, dehydration, infection, alcoholism)	Augmented risk of elevated plasma drug concentration, increased catabolism, inhibition of hepatic drug metabolism
Age (very young [<5 years] and elderly)	Reduced metabolic capacity (greater accumulation of drugs)
Decreased renal and/or hepatic function	Decreased drug clearance/elimination; greater accumulation of drugs or their metabolites
Drug(s) with narrow therapeutic range	Increased risk for dose-related side effects
Female sex	Reduced metabolic capacity, interference with sex hormones
Metabolic or endocrine conditions (eg, fatty liver, obesity, hypothyroidism)	Altered hepatic metabolism, increased body distribution volumes, augmented risk of accumulation for hydrophobic molecules
Polypharmacy (≥3 medications)	Increased risk of metabolic and/or pharmacodynamic interference
Pharmacogenetics	Altered metabolic capacity (greater accumulation of drugs or their metabolites)

MANAGEMENT OF DRUG INTERACTION

The role of pharmacogenetics and ppharmacogenomic

An individual's genetic makeup can alter their response to a drug. Genetics affect pharmacokinetics and pharmacodynamics. Unrecognized mutations can be associated with ADRs or can affect the magnitude of a drug interaction. A common example is the metabolism of ethanol. There are ethnic differences in the metabolism of ethanol by alcohol dehydrogenase. People of Chinese descent have

a higher incidence of atypical alcohol dehydrogenase and therefore become flushed and dizzy when they consume alcohol. Their capacity for consuming alcohol is lower than that for other populations.

To apply pharmacogenetics and pharmacogenomics to the management of drug interactions, it is important to know the difference between the two terms. Pharmacogenetics applies to inherited traits and genetic polymorphisms. Polymorphism refers to stable allelic variations found in the population (occurring at a frequency >1%) that result in altered protein activity. Pharmacogenomics applies to the entire spectrum of genes. With pharmacogenetics, the focus is on metabolizing enzymes and transporters, whereas with pharmacogenomics, the focus is on individualized drug and dosage for a specific disease.

The role of pharmacist in management of drug interaction

The pharmacist, along with the prescriber has a duty to ensure that patients are aware of the risk of side effects and a suitable course of action should they occur. With their detailed knowledge of medicine, pharmacists have the ability to relate unexpected symptoms experienced by patients to possible adverse effects of their drug therapy. The practice in clinical pharmacy also ensures that ADRs are minimized by avoiding drugs with potential side effects in susceptible patients. Thus, pharmacist has a major role to play in relation to prevention, detection, and reporting ADRs.

CONCLUSION :

The past several years have seen major advances in our understanding of DDIs, particularly in the area of the molecular mechanisms by which drug interact. However, our ability to appropriately apply this information to specific patients has lagged far behind. Pharmacists must take responsibility for monitoring for drug interactions and notifying the physician and patient about potential problems.

REFERENCES :

1.Wang Y, Eldridge N, Metersky ML, Verzier NR, Meehan TP, Pandolfi MM et al (2014) National trends in patient safety for four common conditions, 2005-2011. N Engl J Med 370(4):341–35

2.Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC (2016) Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. JAMA Intern Med 176:473–482

3.U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion (2014) National action plan for adverse drug event prevention. Author, Washington.

4.Plank-Kiegele B, Burkle T, Muller F, Patapovas A, Sonst A, Pfistermeister B et al (2017) Data requirements for the correct identification of medication errors and adverse drug events in patients presenting at an emergency department. Methods Inf Med 56(4):276–282

5.Johnson JA, Bootman JL (1995) Drug-related morbidity and mortality. A cost-of-illness model. Arch Intern Med 155(18):1949–1956

6.Chen F, Hu ZY, Jia WW, Lu JT, Zhao YS (2014) Quantitative evaluation of drug-drug interaction potentials by in vivo information- guided prediction approach. Curr Drug Metab 15(8):761–766

7.Varma MV, Pang KS, Isoherranen N, Zhao P (2015) Dealing with the complex drug-drug interactions: towards mechanistic models. Biopharm Drug Dispos 36(2):71–92

8.Rinner C, Grossmann W, Sauter SK, Wolzt M, Gall W (2015) Effects of shared electronic health record systems on drug-drug interaction and duplication warning detection. Biomed Res Int 2015:380497

9.Kinch MS, Haynesworth A, Kinch SL, Hoyer D (2014) An overview of FDA-approved new molecular entities: 1827-2013. Drug Discov Today 19(8):1033–1039

10. Pai MP, Bertino JS Jr (2014) Tables of antimicrobial agent pharmacology. In: Mandell GLBJ, Dolin RL, Blaser M (eds) Principles and practice of infectious diseases, 8th edn. Elsevier, Philadelphia, PA,

11. Silver LL (2011) Challenges of antibacterial discovery. Clin Microbiol Rev 24(1):71–109

12. Mudie DM, Amidon GL, Amidon GE (2010) Physiological parameters for oral delivery and in vitro testing. Mol Pharm 7(5):1388–1405

13. Al-Kassas R, Bansal M, Shaw J (2017) Nanosizing techniques for improving bioavailability of drugs. J Control Release 260:202–212

14. Tatro DS (1972) Tetracycline-antacid interactions. JAMA 220(4):586

15. R, Echizen H (2011) Clinically significant drug interactions with antacids: an update. Drugs 71(14):1839–184

16. Laksitorini M, Prasasty VD, Kiptoo PK, Siahaan TJ (2014) Pathways and progress in improving drug delivery through the intestinal mucosa and blood-brain barriers. Ther Deliv 5(10):1143–1163

17. Linnankoski J, Makela J, Palmgren J, Mauriala T, Vedin C, Ungell AL et al (2010) Paracellular porosity and pore size of the human intestinal epithelium in tissue and cell culture models. J Pharm Sci 99(4):2166–2174

18. Matsson P, Doak BC, Over B, Kihlberg J (2016) Cell permeability beyond the rule of 5. Adv Drug Deliv Rev 101:42–61

19. Van Waterschoot RA, Schinkel AH (2011) A critical analysis of the interplay between cytochrome P450 3A and P-glycoprotein: recent insights from knockout and transgenic mice. Pharmacol Rev 63(2):390–410

20. Caldwell J, Gardner I, Swales N (1995) An introduction to drug disposition: the basic principles of absorption, distribution, metabolism, and excretion. Toxicol Pathol 23(2):102–114

21. Benet LZ, Izumi T, Zhang Y, Silverman JA, Wacher VJ (1999) Intestinal MDR transport proteins and P-450 enzymes as barriers to oral drug delivery. J Control Release 62(1–2):25–31

22. Fung KW, Kapusnik-Uner J, Cunningham J, Higby-Baker S, Bodenreider O (2017) Comparison of three commercial knowledge bases for detection of drug-drug interactions in clinical decision support. J Am Med Inform Assoc 24(4):806–812

23. De Clercq E, Li G (2016) Approved antiviral drugs over the past 50 years. Clin Microbiol Rev 29(3):695–747

24. Seiple IB, Zhang Z, Jakubec P, Langlois-Mercier A, Wright PM, Hog DT et al (2016) A platform for the discovery of new macrolide antibiotics. Nature 533(7603):338–345

25. Yan M, Baran PS (2016) Drug discovery: fighting evolution with chemical synthesis. Nature 533(7603):326–327

26. Chan L. Applying the knowledge of pharmacogenetics and pharmacogenomics in the management of drug interactions. Program and abstracts of The American Society of Health-System Pharmacists Midyear Clinical Meeting 2000; December 7, 2000; Las Vegas, Nevada. Abstract 3713020.

27.Palanisamy S, Arul Kumaran KS, Rajasekaran A. A study on assessment, monitoring, documentation and reporting of adverse drug reactions at a multi-specialty ertiary care teaching hospital in South India. Int J PharmTech Res. 2009;4:1519–22.

28. Hazlet TK, Lee TA, Hansten PD, Horn JR. Performance of community pharmacy drug interaction software. J Am Pharm Assoc (Wash) 2001;41:200–4.

29. Doucet J, Chassagne P, Trivalle C, Landrin I, Pauty MD, Kadri N, et al. Drug-drug interactions related to hospital admissions in older adults: A prospective study of 1000 patients. J Am Geriatr Soc. 1996;44:944–8.

30.Orloff DG. Label changes for Simvastatin (Zocor) US Food and Drug Administration. 2002

31. Chrischilles EA, Fulda TR, Byrns PJ, Winckler SC, Rupp MT, Chui MA. The role of pharmacy computer systems in preventing medication errors. J Am Pharm Assoc (Wash) 2002;42:439–48.

32. Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. Clin Pharmacokinet. 2002;41:343–70. [

33. Pasternak RC, Smith SC, Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol. 2002;40:567–72.

34. Ogbru O. Drug-food interactions. Clin Trends Pharm Pract. 1996;10:53–60.