



REVIEW

# Drug safety: The concept, inception and its importance in patients' health



Thamir M. Alshammari \*

College of Pharmacy, Hail University, Hail, Saudi Arabia  
Medication Safety Research Chair, King Saud University, Riyadh, Saudi Arabia

Received 9 January 2014; accepted 28 April 2014  
Available online 9 May 2014

## KEYWORDS

Drug safety;  
Special populations;  
Adverse drug reaction;  
Minimizing adverse drug  
reaction

**Abstract** *Background:* Drug safety is one of the hottest topics in daily medical practice, particularly with regard to approving new medication or questioning the possibility of withdrawing a drug from the market.

*Aim:* The aim of this review is to highlight the importance of the drug safety concept and its impact on patients' health.

*Methods:* A literature search was conducted using Pubmed®, EMBASE®, EBSCO and Medline in the period between 1980 and 2013. The terms used in the search included “Drug Safety”, “Medication Safety”, “Patient Safety”, “Drug Interaction”, “Drug Pharmacokinetic”, and “Adverse Drug Reaction”. All retrieved abstracts were evaluated within the context of the review objectives. The full texts of the selected articles were included in this review. Studies in non-English language were excluded in this review.

*Results:* Since the early days of the past century, many acts, laws, or amendments have been created to make sure that approved drugs are first safe and then effective. Furthermore, these regulations are continuing to change to make sure that these drugs have a positive benefit–risk balance. Personalized medicine should be considered when medications are given to patients because the pharmacokinetic process inside the body varies from patient to patient and from one specific disease state to another. However, adverse drug reactions can be minimized if more precautions are taken by healthcare professionals, especially including the patient as one pillar of the therapeutic plan and providing more patient counseling, which will improve drug safety.

*Conclusion:* The drug safety concept has earned a lot of attention during the past decade due to the fact it plays a major role in patients' health. Recent laws stress this concept should be included

\* Address: Hail University, College of Pharmacy, Department of Clinical Pharmacy, P.O. Box 6166, Horan Street, Hail City 81442, Saudi Arabia. Tel.: +966 505192886.

E-mail addresses: [Thamer.alshammari@gmail.com](mailto:Thamer.alshammari@gmail.com), [Th.alshammari@uoh.edu.sa](mailto:Th.alshammari@uoh.edu.sa)

Peer review under responsibility of King Saud University.



Production and hosting by Elsevier

in the process of new medications' approval and continued conduct of post-marketing drug evaluations. Benefit–risk assessment should be considered by all health care professionals when they need to give specific drugs to specific groups of patients. Therefore, more care should be given to some patients, such as pregnant women, children and the elderly, since they are considered vulnerable populations.

© 2014 King Saud University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

## Contents

1. Background and history . . . . .	406
2. Methods . . . . .	406
3. Drug safety facts . . . . .	407
4. Specific patient populations and drug safety . . . . .	407
4.1. Pregnant and lactating women . . . . .	407
4.2. Children (pediatrics) . . . . .	407
4.3. Old people (geriatrics) . . . . .	408
5. Drug safety and drug–drug and food–drug interaction . . . . .	408
6. Minimizing drug side effects . . . . .	409
7. Conclusion . . . . .	410
Conflict of interest . . . . .	410
References . . . . .	410

## 1. Background and history

The concept of drug safety, also called “Medication Safety”, is not new, especially in the developed countries in the field of health. For instance, we find in the United States of America (USA) an experience for more than a century in the field of the safety of medications, and the use of these drugs led to creation of new acts or changes to the existing ones. For example, in October 1937, the use of the antibiotic sulfanilamide caused the death of more than 100 people in the USA. These deaths were not due to the active ingredient itself; rather, they were caused by the addition of diethylene glycol (DEG), the excipient used as a solvent for the active drug. DEG was supposed to be inert, with no therapeutic benefits; however, it was the toxic substance that led to those fatal side effects. The company claimed they did not foresee these side effects, which was true, as they did not commit animal studies before they marketed the drug. Because of this incident, the U.S. Food and Drug Administration (FDA) approved an act to ensure the safety of any drug by conducting non-clinical and clinical studies before the drugs are marketed for public use (Geiling and Cannon, 1938; Young, 1984; Wax, 1995).

Of course, the problems arising from drugs and their side effects did not stop occurring. A severe worldwide crisis was initiated by the use of the drug thalidomide, which was used as an antiemetic agent for pregnant women in many countries. In the early 1960s, the use of thalidomide during the first trimester of pregnancy led to teratogenic effects manifested by the birth of infants with severe deformities known as “Phocomelia”. Babies would be born lacking extremities (hands and legs) or with only very short ones. Many infants died because of this “medication” as well. Overall, more than 10,000 children in 46 countries were victims of thalidomide. It is important to mention that this drug was not authorized or

approved for use in the United States because of some concerns that arose during non-clinical studies (animal studies) due to the existence of cases of deformities on animal embryos. Note that those animal studies were conducted according to the act that was initiated following the sulfanilamide incident in the USA; therefore the public was protected and avoided from this crisis (Ito et al., 2011; Kim and Scialli, 2011; Martinez-Frias, 2012).

Up until now, there are drugs that could be taken off the market or withdrawn due to safety issues concerning their relation with the emergence of serious side effects, such as the recent withdrawal of the anti-diabetic agent rosiglitazone (Avandia®) from the global market as a result of its relationship with the incidence of heart attacks. Therefore, we find the concept of drug safety a very important and comprehensive concept that is considered a priority with regard to the use of medications. Actually, this concept can be considered an integrated science in itself that involves many other scientific aspects, such as the side effects of drugs, the quality of medications, medical errors in the use of drugs, lack of efficacy of drugs, and counterfeit drugs (Psaty and Furberg, 2007a,b; Hiatt et al., 2013). In Saudi Arabia, there is a need to educate and enhance the knowledge of healthcare professionals regarding the concept of drug safety since many studies that have been conducted in Saudi Arabia found that there is a lack of culture of drug safety in Saudi Arabia among all levels of healthcare professionals (Aljadhey et al., 2014; Khan, 2013; Mahmoud et al., 2014).

## 2. Methods

A search of several databases (Pubmed®, EMBASE®, EBSCO and Medline) was carried out in the period between 1980 and 2013. Several terms were used in the search, including

“Drug Safety”, “Medication Safety”, “Patient Safety”, “Drug Interaction”, “Drug Pharmacokinetic”, and “Adverse Drug Reaction”. All retrieved abstracts were evaluated within the context of the review objectives and only studies in English language were included in this review. The full texts of the selected articles were included in this review.

### 3. Drug safety facts

All drugs have side effects, but the extent of their impact and severity varies from mild (such as mild itching or mild headache) to severe (such as severe rash, damage to vital organs, primarily the liver and kidneys, and possibly even death). Most of the side effects are predictable and mentioned in the leaflets for each drug. However, the serious problem is that some of the drugs' side effects are not previously known or have not been noticed, and the real risk here is whether they would exert a severe deleterious impact on the patients who are using them. Among the factors that may increase the severity of the side effects, the type of medications and the type of patients using them are the most important (Gholami and Shalviri, 1999; Hilmer et al., 2007).

Some drugs may not cause serious symptoms, such as certain types of antibiotics; other medications may cause serious symptoms, such as certain cancer drugs, anti-diabetic medications, medications to control elevated blood lipids, and many others. Nonetheless, serious adverse reactions can arise from widely used and well-known medications. For example, many people might believe that paracetamol, which is sold as Panadol®, Fevadol®, Tylenol® and under other trade names, is very safe and would not cause serious side effects. However, this drug can induce dangerous side effects at high doses, particularly ones affecting the liver. What makes this worse is that the drug is found in many combinations used for cold and flu, and the patient might be unaware of this and take extra doses, leading to a direct liver injury (Larson, 2007; Chun et al., 2009; Bunchorntavakul and Reddy, 2013).

### 4. Specific patient populations and drug safety

The type of patients using medications is a very important factor in considering drugs' side effects. People vary in their responses to medications according to their age (Crooks and Stevenson, 1981). In addition, responses to drugs vary between males and females due to the physiological differences between genders (Xie et al., 1997; Beierle et al., 1999; Franconi et al., 2007). In addition, there are patient groups that need greater attention and care when using medications, such as pregnant women, the elderly, and children (Sannerstedt et al., 1996).

#### 4.1. Pregnant and lactating women

Each phase of pregnancy, which lasts nine months, is considered important and critical during the use of any medication. Pregnancy is divided into three major trimesters: the first trimester (the first three months), the second trimester (the second three months), and the third trimester (the last three months of pregnancy). As mentioned earlier, all these trimesters are important periods; therefore, a pregnant woman must not take any medication without consulting a specialist (a physician or a pharmacist) about the safety of the medication as it

may affect the formation of the fetus, as was the case with the use of thalidomide, as mentioned above.

The danger of effects of drugs is not limited to taking drugs during pregnancy: deleterious effects on the fetus may be experienced even if a medication is taken within a short time period before pregnancy (perhaps several weeks) (Dai et al., 1989; Schaefer et al., 2010). For example, the drug isotretinoin (Roaccutane®), used for the treatment of acne, is considered one of the most dangerous medications during pregnancy as it has teratogenic effects on the fetus; therefore it is contraindicated during pregnancy. Thus, with the use of this drug, it is important to consult and advise women not to become pregnant even after cessation of drug use. This could occur by informing them of the matter and advising them to consider the possibility of using contraception. Also, during the period of lactation, mothers should consult professionals before use of any medication because some medications can be excreted in breast milk, which may have a negative impact on the infant. These warnings should not be applied only to chemically synthesized drugs, but should also be considered while using any herbal medicines or anything that is taken or used as a medicine (Dumont and Black, 2013).

#### 4.2. Children (pediatrics)

The second category to consider, which is no less important than the category of pregnant women, is children. It is crucial to take extreme caution when using any medications for children as many medications are divided depending on age group – some medications are contraindicated in patients less than 18 years or less than 12 years old, and also some medications are contraindicated for use in children less than two years old. The reasons include mostly the lack of scientific studies and clinical trials needed to evaluate the safety of these medications in each age group separately. In addition, children's vital organs are not mature, and thus exposure to certain medications may lead to toxic side effects as the body is mostly unable to fully metabolize or excrete the drugs. This would lead to the presence of active compounds in the body for an extended period of time as well as an increase in their levels in the body, inducing toxic effects (Ryan et al., 2008; Vassilev et al., 2010; Adefurin et al., 2011; Yang and So, 2013). This can usually be avoided by adjusting the dose but, as mentioned earlier, the lack of clinical studies to evaluate the pharmacokinetic profile of these drugs makes it difficult to adjust the dose; thus many drugs are not recommended for use in certain age groups.

Furthermore, it is crucial to use medications in this age group in the exact dose prescribed or recommended, as deviation from that dose may lead to severe side effects if increased or would render the drug ineffective, imposing a danger on children as the disease is not being treated effectively. What also contributes to this problem is that a drug can be formulated in different dosage forms. For example, a medication can be formulated in the form of syrups, tablets, capsules, and suppositories. This may have an impact as each dosage form has a different pharmacokinetic profile, especially as regards their absorption rate – e.g., syrups have faster absorption than tablets or suppositories – and thus the dose should be taken as prescribed by the physician and reviewed by the pharmacist (Levy, 1964; Vogt et al., 1994).

It is important that all pharmaceutical companies provide a measuring tool with liquid preparations that are administered orally to ensure exact and correct doses at every use. Preferred measuring tools would be divided into milliliters. For example, plastic syringes are excellent choices for administering syrups to children. They are better than measuring caps as they are easier to handle and can provide precise and accurate dosing (Madlon-Kay and Mosch, 2000; Sobhani et al., 2008; Ryu and Lee, 2012; Spiegel et al., 2013). If a medication is only available in the form of tablets or capsules, it is preferable to consult a pharmacist about the proper way to use the drug and how it should be administered to children. Tablets are usually advised to be taken with ample quantities of juice or water. Also, if tablets will be taken with food, it is important to know if the tablet could be subject to drug–food interaction and the pharmacist should provide the proper advice.

Aspirin, or “acetylsalicylic acid”, which is widely used as an analgesic and antipyretic, is one of the drugs that are safely used in adult groups but contraindicated in children, as it could lead to a severe adverse effect known as “Reye’s Syndrome”. Thus, a safer alternative to be given to children would be paracetamol and ibuprofen in the correct adjusted dose and based on weight as well (Boucher and Beaulac-Baillargeon, 2006; Selves et al., 2013).

It is important to consider the weight of the child while prescribing medications and their doses, as the dosages of most drugs used for children are calculated based on the weight of the child. The storage of pediatric medications is important as well. Every dispensed drug is accompanied by instructions for proper storage, such as the suitable recommended temperature for that purpose. There are some important instructions that may be overlooked by parents, such as making sure the medications have not expired. Also families need to be very careful with medications in general and be aware that they must be kept out of reach of children to prevent accidental ingestion, which could be fatal in many situations.

#### 4.3. Old people (geriatrics)

The geriatric group is considered to be most vulnerable to the effect of medications and so it is very important to consider their health status before prescribing any medication, for several reasons. The physiological functions of many body organs decline with age, especially important organs such as the liver and kidneys. Older people may also suffer from dementia or “impaired memory” and so forget to take their medications (Wright and Warpula, 2004; Arlt et al., 2008; Toba, 2011; Dhikav et al., 2013; Haider et al., 2013). Older people can suffer from many chronic illnesses, such as high blood pressure, diabetes, and high blood cholesterol and lipids, possibly necessitating the chronic use of multiple medications, which may conflict with each other – what is known as drug–drug interaction. Depending on the type of interaction between drugs, it is possible that the drug level in the plasma would increase too much, leading to toxicity and severe adverse reactions. The opposite can be true as well – the drug may be in low plasma concentrations, exposing the patient to dangers and complications of the illness that was supposed to be controlled by that drug. (Jankel and Speedie, 1990; Ansari, 2010; Hines and Murphy, 2011) Geriatric patients might take more than 16 different medications daily, which makes the chance of the inci-

dence of drug–drug interaction very high, especially if they then take OTC medications without consulting their doctor or pharmacist. In addition, older patients tend to try and use herbal extracts, for which there are not enough scientific data about components which may be dangerous or which could interact with their prescribed medications. This could worsen the conditions they suffer from, such as chronic, heart, liver and kidney diseases. Also, certain types of food may interact with the prescribed medications, with the same outcomes as those mentioned regarding drug–drug interactions, but with different mechanisms (Fugh-Berman and Ernst, 2001; Schmidt and Dalhoff, 2002; Fujita, 2004; Heuberger, 2012).

The incidence of side effects can be easily avoided by applying certain preventive measures on the part of the patient. One of these measures is full awareness and knowledge about the medications used, and this can be achieved by reading the leaflet included in the package of the drug, which usually contains all the necessary information about the drug. The patient can also consult the pharmacist or the doctor for better explanations if needed. As healthcare professionals are usually very busy, it is recommended that the patient should prepare his/her inquiries in advance and write them down, and then present them to their doctor or pharmacist. The patient should also bring all his/her medications with him/her to all appointments with either the doctor or the pharmacist in order that the professional can avoid dispensing drugs that may interact with each other. In addition, it is preferable that old people utilize the assistance available in pharmacies to organize and arrange the administration of their medications correctly. Also it is necessary for every patient to be honest and frank when providing information to their health care professionals. For example, many patients may hide that they drink alcohol. Alcohol affects metabolism greatly and thus may lead to toxicity when taken with drugs prescribed in the normal dosage regimen. Last, the patient must understand and learn the proper method and use of medications to avoid misuse of the drug, which may lead to either side effects or lack of efficacy and benefit. One may use the previously mentioned methods of prevention for any patient, whether the elderly or the others.

It is important to point out that the concepts of drug safety and the proper use of medications are not limited to a certain class of patient or medication users, but are applied to any person who uses a medication.

#### 5. Drug safety and drug–drug and food–drug interaction

Different medications can interact with each other and cause what is known as drug interactions, which can occur with almost all drugs. Such interactions could occur at any stage while the drug is present within the body. These interactions could either reduce or increase the effect of other drugs, or could produce a different, new effect. Drug interactions can occur in any pharmacokinetic (PK) process, including absorption, distribution, metabolism, and excretion. All these PK processes are important and it is therefore crucial that patients should consult a physician or pharmacist about the possible interactions that may occur between drugs and with certain foods to avoid undesirable effects (Karch and Lasagna, 1975).

There are many occasions when drugs may interact with each other in absorption – one such has been observed with

the antihyperlipidemic agent colestipol (Colestid®), which interacts with other medications by decreasing their absorption and thus reducing their effect as their concentrations in the plasma are lowered. (Bays and Dujovne, 1998) Also, iron-containing products which are used for treatment of certain types of anemia can decrease absorption of other drugs, and so it is recommended these drugs are used at least two hours apart. In addition, some types of food may interact with certain medications. For example, calcium-containing foods such as milk and cheese can chelate and form large complex molecules with the antibiotic group tetracyclines, preventing their absorption in the gastrointestinal tract (GIT) and rendering them ineffective in combating infection (Schmidt and Dalhoff, 2002).

The second phase of pharmacokinetics in which medications may interact with each other is the distribution phase. Many drugs are bound to proteins in the plasma, such as albumins and globulins. Protein-bound drugs are not effective and the free plasma concentration of a drug is the active one. Bound and unbound forms of a drug exist in balance with each other and portions of the bound drug are released from their proteins as the free unbound drugs get involved in the rest of the pharmacokinetic processes, including excretion. What can happen is that some drugs may displace other drugs from their proteins, increasing their free unbound concentration in the plasma – leading to adverse effects and signs of toxicity under a normal dosage regimen. For example, the anticoagulant agent warfarin (Coumadin®) is a highly protein-bound drug (97%), meaning that only 3% of the dose is active for biological effects. The widely used antipyretic agent aspirin can displace warfarin from plasma proteins, leading to serious bleeding. Thus, it is very important to be vigilant about this fact, responding by either providing a different antipyretic agent that does not displace warfarin or by adjusting the warfarin dose (lowering the dose) to prevent serious side effects (Zibaenezhad et al., 2004; Ageno et al., 2012; Prankevicene et al., 2013).

The metabolism is one of the most important pharmacokinetic processes and can have great involvement in drug–drug or drug–food interactions. The liver produces many enzymes that are mainly responsible for deactivating xenobiotic agents, including the medications we use. Many drugs can alter liver enzymes by either increasing their expression or lowering their expression and production. The best known drugs that induce liver enzymes are the antibiotic drug rifampicin (Rifampin®) and the antiepileptic agent phenytoin (Dilantin®) (Lehtinen et al., 2013; Yamashita et al., 2013). Well-known and widely used drugs that are liver enzyme inhibitors include the antibiotics erythromycin (Ery-Tab®) and azithromycin (Zithromax®), and the antifungal ketoconazole (Nizoral®). A controversial drug–drug interaction related to induction of microsomal liver enzymes is that observed with the co-administration of antibiotics and contraceptives. Antibiotics reduce the level of the contraceptives and thus they may fail to prevent pregnancy (Shah et al., 2009; Smith et al., 2012; Quinney et al., 2013).

The last stage of pharmacokinetics at which drug interactions may occur is the excretion phase. This could happen when the transporters or the mechanisms by which a drug is excreted are the same for another drug that is concomitantly administered, leading to a delay in the excretion of one of the drugs and increasing its concentration in the body, which can result in toxicity and side effects. An example of such interaction is that

observed when aspirin and the anticancer drug methotrexate (Trexall®) are co-administered (Tracy et al., 1992; Bannwarth et al., 1996; Iqbal et al., 1998; Vakily et al., 2005).

Food–drug interactions can frequently happen and they can be very serious. For example, tyramine-rich food such as cheese, red meat, and excessive amounts of chocolate can interact with the specific antidepressant group of monoamine oxidase inhibitor (MAO-I) drugs, leading to the possibility of inducing a dangerous hypertensive crisis (McCabe, 1986; Livingston and Livingston, 1996; Tipton, 1997; Corti and Taegtmeier, 2012). Some foods are well known for their effect in inducing or inhibiting liver enzymes. Grapefruit juice is a potent inhibitor of CYP450 enzymes that are important in metabolizing certain antihyperlipidemic agents, such as atorvastatin (Lipitor®), lovastatin (Mevacor®), and simvastatin (Zocor®), and hence increase their levels in the body, leading to side effects and toxicity (Fukazawa et al., 2004; Karch, 2004; Ando et al., 2005; Reddy et al., 2011). On the other hand, the herbal extract St. John's wort, which is used as an antidepressant agent, is a potent liver enzyme inducer that would lower the concentrations of drugs such as digoxin, leading to reduction in its efficacy and worsening of the congestive heart failure disease which digoxin is used for. In addition, many calcium and iron-containing foods can impair the absorption of other drugs, as I have described above with specific examples (Johne et al., 1999; Markowitz and DeVane, 2001; Mueller et al., 2004).

Every patient or medication user must ensure they are aware of all necessary information regarding those drugs, as well as the possibility of interactions with other drugs or certain food types, through consulting the pharmacist or physician. This should be done to avoid any potential risks or adverse effects, as well as for proper control of their disease or illness. Groups that are at extreme risk and exposure to those drug interactions include:

- Patients who use multiple medications, especially six or more medications.
- Elderly patients (geriatrics).
- Patients with multiple chronic diseases and illnesses, such as heart disease, diabetes, or hyperlipidemia.
- Patients who use medications that could produce serious side effects and have narrow therapeutic index, such as the anticoagulant agent warfarin, the antiepileptic phenytoin, and certain heart failure medications including digoxin.

## 6. Minimizing drug side effects

As previously stated, each drug has its side effects; however, it is possible to avoid these side effects by using the drug in the proper way, and by following the instructions included in the drug leaflet or provided by the pharmacist or the physician. Knowing the necessary information about a medicine is considered the first step in avoiding side effects. For example, when a patient knows that a drug should not be taken at a certain time or with another drug, he/she can avoid the incidence of inappropriate drug interactions and gain the full benefit from his/her medications. Similarly, when a patient knows that he/she should not take a particular drug with food or certain types of it, again his/her medications will be efficacious, with minimal adverse reactions. When a pregnant woman knows

she must not take any medication before consulting the doctor or pharmacist, then she will avoid deleterious effects that may be induced by teratogenic medications and will continue with a safe pregnancy.

Some questions and points considered during patient counseling that are usually raised by healthcare professionals include:

- Should the patient avoid taking a certain medication with other medications?
- Should the patient avoid taking it with certain food or beverages?
- What are the expected side effects of the drugs?
- The medical team should encourage the patient to mention over-the-counter (OTC) medications bought directly from the pharmacy without a prescription, such as cough and cold medications including paracetamol or aspirin.
- The medical team should encourage the patient to bring all his/her medications when he/she goes to see his/her physician.
- The medical team should counsel the patient about all herbal medications that he/she uses, as well as vitamins and dietary supplements.
- The patient should feel comfortable in asking the physician or the pharmacist how his/her drugs work to produce their medical effects.
- Patients should be informed about the proper use of the medications; how many/much, how many times a day, and for how long.
- Patients should be informed regarding the proper uses of injectable medications such as insulin injections.
- The medical team should provide all information required by patients regarding the proper storage of medications, as there are many drugs that are affected by exposure to light or storage at inappropriate temperatures.
- The patient should ask his/her physician or pharmacist about the active ingredients in OTC medications, as some may contain paracetamol and using multiple medications may lead to the ingestion of extra doses, resulting in liver damage.

## 7. Conclusion

Drug safety is the main aspect of medical therapy that can play a major role in deciding which drug should be given to a patient. Also, considering the concept of benefit–risk balance, we found that drugs with a high risk profile should be avoided unless needed. Drug safety has gone through different stages from the last century and till now and there have been several tragedies that we should learn from to protect our patients. All patients should be protected; nevertheless, specific groups of patients should be given more care, such as pregnant women, children, and the elderly, since they are considered vulnerable populations. Drugs can react with other drugs or foods used on a daily basis and specific precautions are required to avoid these simple but dangerous interactions. However, the risks from medications could be minimized through patient education about drug safety and openness with the patient, allowing him/her to ask questions related to their disease or medications. A good relationship between the medical team and the patient is one of the most important determinants for drug safety.

## Conflict of interest

The author has no conflict of interest to declare.

## References

- Adefurin, A., Sammons, H., et al, 2011. Ciprofloxacin safety in paediatrics: a systematic review. *Arch. Dis. Child.* 96 (9), 874–880.
- Agno, W., Gallus, A.S., et al, 2012. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141 (2 Suppl.), e44S–e88S.
- Aljadhey, H., Mahmoud, M.A., et al, 2014. Challenges to and the future of medication safety in Saudi Arabia: a qualitative study. *Saudi Pharm. J.* 22 (4), 326–332.
- Ando, H., Tsuruoka, S., et al, 2005. Effects of grapefruit juice on the pharmacokinetics of pitavastatin and atorvastatin. *Br. J. Clin. Pharmacol.* 60 (5), 494–497.
- Ansari, J., 2010. Drug interaction and pharmacist. *J. Young Pharm.* 2 (3), 326–331.
- Arlt, S., Lindner, R., et al, 2008. Adherence to medication in patients with dementia: predictors and strategies for improvement. *Drugs Aging* 25 (12), 1033–1047.
- Bannwarth, B., Pehourcq, F., et al, 1996. Clinical pharmacokinetics of low-dose pulse methotrexate in rheumatoid arthritis. *Clin. Pharmacokinet.* 30 (3), 194–210.
- Bays, H.E., Dujovne, C.A., 1998. Drug interactions of lipid-altering drugs. *Drug Saf.* 19 (5), 355–371.
- Beierle, I., Meibohm, B., et al, 1999. Gender differences in pharmacokinetics and pharmacodynamics. *Int. J. Clin. Pharmacol. Ther.* 37 (11), 529–547.
- Boucher, N., Beaulac-Baillargeon, L., 2006. Pregnancy prevention among women taking isotretinoin: failure to comply with the recommendations. *Can. Fam. Physician* 52, 338–339.
- Bunchornravakul, C., Reddy, K.R., 2013. Acetaminophen-related hepatotoxicity. *Clin. Liver Dis.* 17 (4), 587–607, viii.
- Chun, L.J., Tong, M.J., et al, 2009. Acetaminophen hepatotoxicity and acute liver failure. *J. Clin. Gastroenterol.* 43 (4), 342–349.
- Corti, N., Taegtmeier, A.B., 2012. Clinically important food-drug interactions: what the practitioner needs to know. *Praxis (Bern 1994)* 101 (13), 849–855.
- Crooks, J., Stevenson, I.H., 1981. Drug response in the elderly—sensitivity and pharmacokinetic considerations. *Age Ageing* 10 (2), 73–80.
- Dai, W.S., Hsu, M.A., et al, 1989. Safety of pregnancy after discontinuation of isotretinoin. *Arch. Dermatol.* 125 (3), 362–365.
- Dhikav, V., Singh, P., et al, 2013. Medication adherence survey of drugs useful in prevention of dementia of Alzheimer's type among Indian patients. *Int. Psychogeriatr.* 25 (9), 1409–1413.
- Dumont, T., Black, A., 2013. Pregnancy and isotretinoin therapy. *CMAJ* 185 (6), 508.
- Franconi, F., Brunelleschi, S., et al, 2007. Gender differences in drug responses. *Pharmacol. Res.* 55 (2), 81–95.
- Fugh-Berman, A., Ernst, E., 2001. Herb-drug interactions: review and assessment of report reliability. *Br. J. Clin. Pharmacol.* 52 (5), 587–595.
- Fujita, K., 2004. Food-drug interactions via human cytochrome P450 3A (CYP3A). *Drug Metabol. Drug Interact.* 20 (4), 195–217.
- Fukazawa, I., Uchida, N., et al, 2004. Effects of grapefruit juice on pharmacokinetics of atorvastatin and pravastatin in Japanese. *Br. J. Clin. Pharmacol.* 57 (4), 448–455.
- Geiling, E.M.K., Cannon, P.R., 1938. Pathologic effects of elixir of sulfanilamide (diethylene glycol) poisoning. A clinical and experimental correlation: final report. *JAMA* 111 (10), 919–926.
- Gholami, K., Shalviri, G., 1999. Factors associated with preventability, predictability, and severity of adverse drug reactions. *Ann. Pharmacother.* 33 (2), 236–240.

- Haider, B., Schmidt, R., et al, 2013. Medication adherence in patients with dementia: an Austrian cohort study. *Alzheimer Dis. Assoc. Disord.*
- Heuberger, R., 2012. Polypharmacy and food-drug interactions among older persons: a review. *J. Nutr. Gerontol. Geriatr.* 31 (4), 325–403.
- Hiatt, W.R., Kaul, S., et al, 2013. The cardiovascular safety of diabetes drugs—insights from the rosiglitazone experience. *N. Engl. J. Med.* 369 (14), 1285–1287.
- Hilmer, S.N., McLachlan, A.J., et al, 2007. Clinical pharmacology in the geriatric patient. *Fundam. Clin. Pharmacol.* 21 (3), 217–230.
- Hines, L.E., Murphy, J.E., 2011. Potentially harmful drug-drug interactions in the elderly: a review. *Am. J. Geriatr. Pharmacother.* 9 (6), 364–377.
- Iqbal, M.P., Baig, J.A., et al, 1998. The effects of non-steroidal anti-inflammatory drugs on the disposition of methotrexate in patients with rheumatoid arthritis. *Biopharm. Drug Dispos.* 19 (3), 163–167.
- Ito, T., Ando, H., et al, 2011. Teratogenic effects of thalidomide: molecular mechanisms. *Cell. Mol. Life Sci.* 68 (9), 1569–1579.
- Jankel, C.A., Speedie, S.M., 1990. Detecting drug interactions: a review of the literature. *DICP* 24 (10), 982–989.
- Johne, A., Brockmoller, J., et al, 1999. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). *Clin. Pharmacol. Ther.* 66 (4), 338–345.
- Karch, A.M., 2004. The grapefruit challenge: the juice inhibits a crucial enzyme, with possibly fatal consequences. *Am. J. Nurs.* 104 (12), 33–35.
- Karch, F.E., Lasagna, L., 1975. Adverse drug reactions. A critical review. *JAMA* 234 (12), 1236–1241.
- Khan, T.M., 2013. Community pharmacists' knowledge and perceptions about adverse drug reactions and barriers towards their reporting in Eastern region, Alahsa, Saudi Arabia. *Ther. Adv. Drug Saf.*
- Kim, J.H., Scialli, A.R., 2011. Thalidomide: the tragedy of birth defects and the effective treatment of disease. *Toxicol. Sci.* 122 (1), 1–6.
- Larson, A.M., 2007. Acetaminophen hepatotoxicity. *Clin. Liver Dis.* 11 (3), 525–548, vi.
- Lehtinen, T., Tolonen, A., et al, 2013. Effects of cytochrome P450 inhibitors and inducers on the metabolism and pharmacokinetics of ospemifene. *Biopharm. Drug Dispos.* 34 (7), 387–395.
- Levy, G., 1964. Effect of dosage form on drug absorption a frequent variable in clinical pharmacology. *Arch. Int. Pharmacodyn. Ther.* 152, 59–68.
- Livingston, M.G., Livingston, H.M., 1996. Monoamine oxidase inhibitors. An update on drug interactions. *Drug Saf.* 14 (4), 219–227.
- Madlon-Kay, D.J., Mosch, F.S., 2000. Liquid medication dosing errors. *J. Fam. Pract.* 49 (8), 741–744.
- Mahmoud, M.A., Alswaida, Y., et al, 2014. Community pharmacists' knowledge, behaviors and experiences about adverse drug reaction reporting in Saudi Arabia. *Saudi Pharm. J.* 22 (5), 411–418.
- Markowitz, J.S., DeVane, C.L., 2001. The emerging recognition of herb-drug interactions with a focus on St. John's wort (*Hypericum perforatum*). *Psychopharmacol. Bull.* 35 (1), 53–64.
- Martinez-Frias, M.L., 2012. The thalidomide experience: review of its effects 50 years later. *Med. Clin. (Barc)* 139 (1), 25–32.
- McCabe, B.J., 1986. Dietary tyramine and other pressor amines in MAOI regimens: a review. *J. Am. Diet. Assoc.* 86 (8), 1059–1064.
- Mueller, S.C., Uehleke, B., et al, 2004. Effect of St John's wort dose and preparations on the pharmacokinetics of digoxin. *Clin. Pharmacol. Ther.* 75 (6), 546–557.
- Pranckeviciene, G., Kadusevicius, E., et al, 2013. Influence of coadministration of antithrombotic medicines, warfarin, and NSAIDs on heparin safety: data from a prospective observational study. *J. Manag. Care Pharm.* 19 (6), 478–486.
- Psaty, B.M., Furberg, C.D., 2007a. The record on rosiglitazone and the risk of myocardial infarction. *N. Engl. J. Med.* 357 (1), 67–69.
- Psaty, B.M., Furberg, C.D., 2007b. Rosiglitazone and cardiovascular risk. *N. Engl. J. Med.* 356 (24), 2522–2524.
- Quinney, S.K., Malireddy, S.R., et al, 2013. Rate of onset of inhibition of gut-wall and hepatic CYP3A by clarithromycin. *Eur. J. Clin. Pharmacol.* 69 (3), 439–448.
- Reddy, P., Ellington, D., et al, 2011. Serum concentrations and clinical effects of atorvastatin in patients taking grapefruit juice daily. *Br. J. Clin. Pharmacol.* 72 (3), 434–441.
- Ryan, T., Brewer, M., et al, 2008. Over-the-counter cough and cold medication use in young children. *Pediatr. Nurs.* 34 (2), 174–180, 184.
- Ryu, G.S., Lee, Y.J., 2012. Analysis of liquid medication dose errors made by patients and caregivers using alternative measuring devices. *J. Manag. Care Pharm.* 18 (6), 439–445.
- Sannerstedt, R., Lundborg, P., et al, 1996. Drugs during pregnancy: an issue of risk classification and information to prescribers. *Drug Saf.* 14 (2), 69–77.
- Schaefer, C., Meister, R., et al, 2010. Isotretinoin exposure and pregnancy outcome: an observational study of the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy. *Arch. Gynecol. Obstet.* 281 (2), 221–227.
- Schmidt, L.E., Dalhoff, K., 2002. Food-drug interactions. *Drugs* 62 (10), 1481–1502.
- Selves, A., Ruiz, S., et al, 2013. Aspirin and its danger: Reye syndrome in young adult. *Ann. Fr. Anesth. Reanim.* 32 (11), 814–816.
- Shah, S.S., Sasaki, K., et al, 2009. Inhibitory effects of ketoconazole, cimetidine and erythromycin on hepatic CYP3A activities in cats. *J. Vet. Med. Sci.* 71 (9), 1151–1159.
- Smith, E.M., Iftikar, F.I., et al, 2012. In vitro inhibition of cytochrome P450-mediated reactions by gemfibrozil, erythromycin, ciprofloxacin and fluoxetine in fish liver microsomes. *Aquat. Toxicol.* 109, 259–266.
- Sobhani, P., Christopherson, J., et al, 2008. Accuracy of oral liquid measuring devices: comparison of dosing cup and oral dosing syringe. *Ann. Pharmacother.* 42 (1), 46–52.
- Spiegel, G.J., Dinh, C., et al, 2013. Design, evaluation, and dissemination of a plastic syringe clip to improve dosing accuracy of liquid medications. *Ann. Biomed. Eng.* 41 (9), 1860–1868.
- Tipton, K.F., 1997. Monoamine oxidase inhibitors and pressor response to dietary amines. *Vopr. Med. Khim.* 43 (6), 494–503.
- Toba, K., 2011. Drug compliance and adherence. *Nihon Rinsho* 69 (Suppl. 10(Pt 2)), 22–25.
- Tracy, T.S., Krohn, K., et al, 1992. The effects of a salicylate, ibuprofen, and naproxen on the disposition of methotrexate in patients with rheumatoid arthritis. *Eur. J. Clin. Pharmacol.* 42 (2), 121–125.
- Vakily, M., Amer, F., et al, 2005. Coadministration of lansoprazole and naproxen does not affect the pharmacokinetic profile of methotrexate in adult patients with rheumatoid arthritis. *J. Clin. Pharmacol.* 45 (10), 1179–1186.
- Vassilev, Z.P., Kabadi, S., et al, 2010. Safety and efficacy of over-the-counter cough and cold medicines for use in children. *Expert Opin. Drug Saf.* 9 (2), 233–242.
- Vogt, D., Trenk, D., et al, 1994. Pharmacokinetics and haemodynamic effects of ISDN following different dosage forms and routes of administration. *Eur. J. Clin. Pharmacol.* 46 (4), 319–324.
- Wax, P.M., 1995. Elixirs, diluents, and the passage of the 1938 Federal Food, Drug and Cosmetic Act. *Ann. Intern. Med.* 122 (6), 456–461.
- Wright, R.M., Warpula, R.W., 2004. Geriatric pharmacology: safer prescribing for the elderly patient. *J. Am. Podiatr. Med. Assoc.* 94 (2), 90–97.
- Xie, C.X., Piccoro, L.T., et al, 1997. Gender-related considerations in clinical pharmacology and drug therapeutics. *Crit. Care Nurs. Clin. North Am.* 9 (4), 459–468.

- Yamashita, F., Sasa, Y., et al, 2013. Modeling of Rifampicin-Induced CYP3A4 activation dynamics for the prediction of clinical drug–drug interactions from in vitro data. *PLoS One* 8 (9), e70330.
- Yang, M., So, T.Y., 2013. Revisiting the safety of over-the-counter cough and cold medications in the pediatric population. *Clin. Pediatr.*
- Young, J., 1984. Sulfanilamide and Diethylene Glycol. *Chemistry and Modern Society*. Emory University, Department of History, Atlanta, GA, Chapter 6, pp. 105–125.
- Zibaenezhad, M.J., Mowla, A., et al, 2004. Warfarin and aspirin versus aspirin alone in patients with acute myocardial infarction: a pilot study. *Angiology* 55 (1), 17–20.