Mediterranean Journal of
Pharmacy & Pharmaceutical Sciences
www.medjpps.com

ISSN: 2789-1895 online
ISSN: 2958-3101 print

ORIGINAL RESEARCH article

Exploration of drug-drug interaction in prescriptions of Libyan practitioners in community pharmacies

Jamila R. Khalil *, **Fatima N. Regaey** and **Suhera M. Aburawi**

Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, University of Tripoli, Tripoli, Libya
*Author to whom correspondence should be addressed

Received: 14-10-2023, **Revised:** 09-11-2023, **Accepted:** 14-11-2023, **Published:** 31-12-2023

HOW TO CITE THIS

Khalil et al. (2023) Exploration of drug-drug interaction in prescriptions of Libyan practitioners in community pharmacies. Mediterr J Pharm Pharm Sci. 3 (4): 18-25. [Article number: 130]. https://doi.org/10.5281/zenodo.10125879

Keywords: Community pharmacy, drug-drug interaction, drug interaction checker, prescription

Abstract: The drug-drug interactions (DDIs) are actions or events that occur when two or more drugs administered together, may cause a clinical significance or not. Certain factors may affect the severity of DDIs such as age, gender, number of drugs prescribed, and physician specialists. This study aims to answer: Is there DDI in Libyan community pharmacies? In addition, to explore the factors that might be affecting DDI. Drug Interactions Checkers are used. 200 prescriptions were collected randomly from two different areas (high and low income),100 from each one and were used to investigate the DDIs by using two different sources (Drugs.com and BNF platforms), bearing in mind, age, gender, prescribers' specialty, and drug number (prescription size). A personal interview questionnaire with pharmacists to investigate a source of DDI knowledge was considered. The correlation test was used to analyze the findings. The randomly selected sample has 316 drug combinations. The study has revealed a minimum of three drugs (46.0%). In general, Drugs.com was the richer source of DDI than BNF (66.5% and 34.5%, respectively). It is found that 66.5% (67.0% of this is moderate DDI) of these combinations have DDI by Drugs.com. A significant correlation between DDI and gender (male > female, p=0.035) was found. In a state of residential areas, the results are similar in both selected pharmacies. Most moderate DDIs (21.0% and 15.0%) are prescribed by orthopedics and psychiatrists, respectively. The observational interview questionnaire indicated that 100% of the participating pharmacists had no source of knowledge regarding DDI, 100% of 200 prescriptions had no chick it regarding DDI and 100% of found DDI is released to use by community pharmacies to patients. More than half of the prescribed drug combinations have DDIs (classified as moderate DDIs), and all of them are released for use by pharmacists.

Introduction

All used drugs have the potential to produce benefits and risks, that particular drug response is affected by its concentration and sometimes its metabolites, at the site of action [1]. This subject is studied under the pharmacokinetic and pharmacodynamics phases. Patients have differences in their response to the same drug, this is related to age, gender, disease, genetics, and the presence of other drugs. Patients have to receive several drugs at the same time, this is because of combination therapy. In addition, the patient may suffer from several conditions, and each one should be treated with one or more drugs. As a result, the potential interactions of

ISSN: 2789-1895 online
ISSN: 2958-3101 print

these drugs will occur within the body which could have no clinical significance, severe interactions due to toxicity, or ineffective therapy by antagonism [1]. Drug-drug interaction (DDI) is a co-administration of two or more drugs. It could decrease or increase the action of some drugs, or cause adverse effects and unintended consequences [2]. During the early 1960s, study showed many drugs enhance or inhibit the metabolism of another drug [3]. In 1965, the first international symposium on drug interactions and their clinical importance was conducted. Accordingly, the DDIs issue became the subject of several symposia and reviews in medical journals. The Swedish Drug Regulatory Agency required the pharmaceutical industry to annual reviews of DDI in the national formulary. Besides that, there was an increasing number of reports concerning DDIs and their metabolic interactions. That leads to increasing development and understanding of sophisticated *in vitro* systems for the investigation of drug biotransformation processes. Many reports of DDIs based on *in vitro* findings of patient-lacked clinical relevance added confusion and some doubt rather than systematic knowledge [3]. Cascorbi [4] suggested problems can be limited by the use of Electronic Prescribing Systems (EPS), which can alert the user early on the possible interactions and can assist in drug selection and dosage form. DDIs lead to desired or/and undesired effects, which can in turn either potentiate or weaken each other [5]. The source of DDI knowledge: Drug-interaction alerting is one of several types of computerized medication-related clinical decision-support (CDS) used to improve patient safety [5] such as different computer platforms such as Drug Interaction Checker (DIC) [6]. In addition, the Personal Digital Assistant (PDA) is frequently used for finding DDIs, and it often derives from familiar textbooks, handbooks, and internet sources that can be updated regularly. It can also be accessible at the point of patient care, because it is easy to use, and is expected to substitute for standard references [7], for example, community pharmacists in Finland are obliged to ensure the safe and appropriate use of prescriptions, and identifying possible DDIs by developed electronic medication risk management databases and tools, such as EBMEDS [8]. The Drug Interaction Checkers was drugs.com database which is an American online website that has many choices about the drugs to assist Health care providers. DDIs classification is derived into four classes, major, moderate, minor and unknown [9]. British National Formulary (BNF), is a printed edition updated twice a year, and there is an online platform updated monthly, trusted by healthcare professionals in the UK and all over the world. The DDIs are classified into four classes, i.e. severe, moderate, mild and unknown [10]. DDIs are one of the most significant problems with prescribed drugs [11]. Several studies pointed out that a prescriber's ability is limited to recognize well-documented DDIs. The prescriber relies on the pharmacist as a key source of DDI information. However, studies indicate that the ability of the pharmacist to identify important drug interactions is also lacking [5]. The high hazard of unwanted DDIs even occurs in developed countries. 20.0% of the adverse drug events responsible for 770,000 deaths are due to DI in the USA. In Sudan, primary health services are not available to the majority of the patients, therefore, the impact of DI will be higher. 95.0% of the dispensers in community pharmacies provided a DI. As a result, it is suggested to ensure the appropriateness of the prescribed medicines [12]. The result of a sub-therapeutic dose can increase the concentration of the drug; therefore, the risk of side effects could be higher [13]. FDA defines the possible result of DI as death, life-threatening, hospitalization (initial or prolonged, disability, permanent change, injury, damage or disruption in the patient's body function/ structure, physical activity, or quality of life. Congenital anomaly, and requires intervention to prevent permanent impairment or damage [14]. Increasing the risks of DDIs with poly-pharmacy [14]. With age, increase in multi-morbidity which necessitates several drugs for one patient at the same time, for example the average 65-year-old patient has five drugs simultaneously, and this could be increased in between 75-84 years-old patients. According to a European study, patients with a mean age of 81 years 34.0% to 68.0% were taking more than five drugs [4], therefore, the possibility of DDIs occurrence is high [15]. According to the WHO, the ADR database contains more than 3.8 million suspected adverse drug reaction reports from 82 countries due to the DDIs [13], accounting for 05.0% to 26.0% of all adverse drug reactions [15]. DDIs are responsible for up to 02.0% to 03.0% of hospital

ISSN: 2789-1895 online
ISSN: 2958-3101 print

admissions [11]. The relationship of age with DDIs, number of drugs with DDIs, and prescribers and DDIs, have been reported [4, 15, 16]. Indeed, cardiologists and dermatologists of physician specialists have direct and indirect relationships, respectively, with DDIs [16]. Males and females have direct and indirect relationships with DDIs [17]. Medication-taking behavior may be affected by traditional consumer choices under a budget constraint in that increased prices lead to decreased utilization. There is a relationship between economic areas (high and low income) and DDIs [18]. Thus, this study aims to estimate the prevalence of major, moderate and minor DDIs in Libyan community pharmacies, and to evaluate the association of these interactions with patient characteristics.

Materials and methods

This study was approved by the Ethical Committee of Scientific Research (ECSR, 0124-2023). It is about investigating DDIs in prescriptions of Libyan practitioners from two community pharmacies and includes the analysis of patient characteristics and prescription size (number of drugs). Descriptive and correlation analysis of DDIs and patient characteristics such as age, gender, source of prescriptions, medical specialties, and prescription size (number of drugs). An interview questionnaire about using databases or platforms to indicate the DDIs at pharmacies. The dispensing behavior of pharmacists to dispense prescribed prescriptions was measured. Over the last June, July, and August 2023, 200 prescriptions were collected from two different pharmacies in different areas of Tripoli city, namely, Khalifa Pharmacy (low income) and Almenshia pharmacy (high income). Thus, 100 prescriptions for each one, and the prescriptions contained at least three drugs. The analysis of DDIs was performed by using the Drug Interactions Checkers from different committee's databases (USA) [9]. BNF was a printed edition that examined the DDIs from Appendix 1-Interactions (UK) [10]. The interview questionnaire included: is there a program desktop used at these two pharmacies as a DDIs checker? No, there are no specific strategies to explore DDIs of prescriptions. Most pharmacists deal alone with different sources such as BNF, reading the medication’s leaflets, or just depending on their knowledge. Does the pharmacist who dispensed the drugs of prescriptions have DDI? Yes, he dispensed all prescriptions. Data was calculated as frequency and percentage. A Person's correlation coefficient was also used.

Results

In this study, using the Pearson correlation coefficient, there is a negative significant correlation between gender and the number of drugs ($r=-0.149$, $p=0.035$). This means that the female has significantly a smaller number of drugs than the male. Alternatively, there is no significant correlation between age and number of drugs ($r=0.072$, $p=0.312$). The number of drugs may correlate with age increase. There is no correlation at all between physician specialists and the number of drugs ($r=0.002$, $p=0.983$), which means, there is no great difference between physician specialists and the number of drugs prescribed. There is no significant of correlation between the source of prescriptions and the number of drugs ($r=0.095$, $p=0.179$), which means there is a relationship between the pharmacies were collected data and the number of drugs. This study investigated 316 DDIs and prepared a list of classified DDIs upon BNF and Drugs.com. These DDIs derived into 164 DDIs (52.0%) in a high residential area (Almenshia pharmacy) and 152 DDIs (48.0%) in a low residential area (Khalifa pharmacy). In **Table 1**, about the Drugs.com database [9], there is 33.5% of investigated DDIs are free from known DDIs. As a result, most of these known DDIs are classified as moderate (44.3%). However, BNF [10] pointed out that 34.4% of investigated DDIs have known DDIs, and most of them are moderate (19.6%) as shown in **Table 2**.

ISSN: 2789-1895 online
ISSN: 2958-3101 print

Table 1: Classifications of the studied DDIs according to Drugs.com [9]

Classification of DDIs	Total number	Percentage
Major	36	11.4
Minor	34	10.8
Moderate	140	44.3
Unknown	106	33.5
Total	**316**	**100**

Unknown: means there are no interactions

Table 2: Classification of the studied DDIs according to the BNF [10]

Classification of DDIs	Total number	Percentage
Unknown	207	65.5
Mild	15	4.7
Moderate	62	19.6
Severe	32	10.1
Total	**316**	**100**

Unknown: means there is insufficient evidence to hazard

As it is shown in **Figure 1**, most interactions are moderate (44.3%). But nearly, an equal percentage between moderate and unknown in the low residential area (18.0%-19.3%, respectively), but it is clear that moderate DDIs more than other classes in the high residential area (25.3%). **In Figure 2**, about gender, most of the participants existed in moderate DDI class, where there were more than female participants. In **Table 3**, most of the participants at age of more than 45 years old. The total result is affected by another age group, where the highest percentage in old adults above 45 is for minors then the moderate DDI classes (73.5%-62.1%, respectively). In **Table 4**, with physician specialists, the highest DDI class is found in the moderate DDI class (n=140). The scattered number of DI by different physician specialists. The highest number is found in orthopedic physicians then psychiatrists at the moderate DDI class (21.0% and 15.0%, respectively).

In **Table 5**, about poly-therapy (prescription size, drug number), 46.2% of the study's samples referred to prescriptions have three drugs with the moderate DDI class (n=45) and major DDI class (n=18). In addition, 34.5% of the prescriptions belong to prescriptions that have four drugs with moderate DDI class (n=51) and major DDI class (n=11). Then small fractions of DDIs 07.28%, 05.3%, 04.7%, 0.95% and 0.95% came from prescriptions that have several drugs of 8, 6, 5, 9 and 7, respectively).

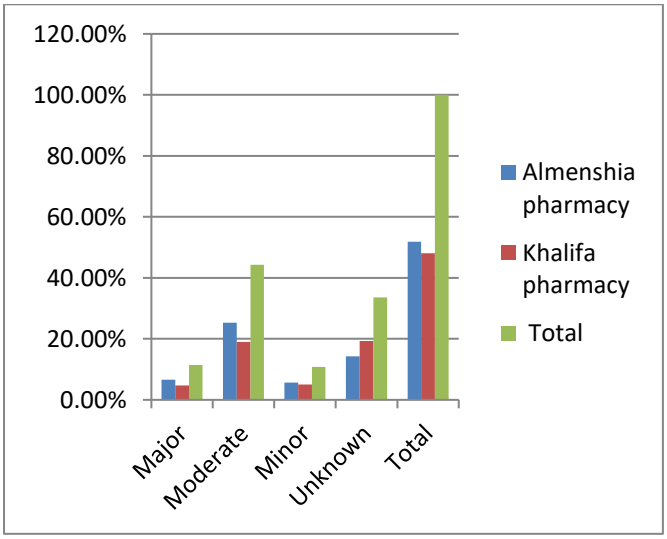

Figure 1: Distribution of different DDI classes upon residential areas

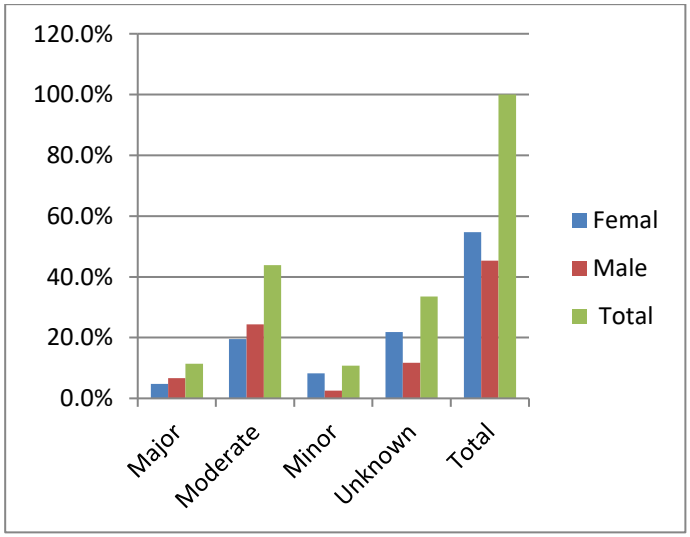

Figure 2: Distribution of different gender on different classes of DDIs

ISSN: 2789-1895 online
ISSN: 2958-3101 print

Table 3: Distribution of participants according to their ages in different DDI class

Classification according to Drugs.om	Infants (<2 years) (%)	Children (2-16 years) (%)	Young adults (>16-30 years) (%)	Middle-aged (31-45 years) (%)	Old adults >45 years (%)	Total DDIs (316) (%)
Major	0	0	5.4	32.4	62.2	11.7
Moderate	0	3.6	13.6	20.7	62.1	44.3
Minor	0	2.9	5.9	17.6	73.5	10.8
Unknown	5.7	11.3	13.2	30.1	39.6	33.5
Total of DDIs (316) (%)	**1.9**	**5.7**	**11.7**	**25**	**56.0**	**100**

Table 4: Physician specialists defined by DDI classification

Physician specialty	Major	Minor	Moderate	Unknown	Total
Blood vessels physician	2	0	1	1	4
Cardiologist	4	4	19	5	32
Dentist	1	0	2	2	5
Dermatologist	0	0	0	4	4
Emergency physician	0	0	1	1	2
Fertility specialist	0	0	0	1	1
General Physician	1	3	8	13	25
Gynecologist	0	1	8	11	20
Internist	0	7	14	14	37
Internist, Orthopedist and Rheumatologist	2	0	0	0	2
Neurologist	1	1	9	0	11
Nutritionist	0	0	0	2	2
Oncologist	2	2	11	4	19
Ophthalmologist	0	0	1	2	3
Orthopedic physician	8	3	29	16	56
Otolaryngologist	0	5	3	12	20
Pediatrician	0	1	0	13	14
Plastic surgeon	0	0	0	1	1
Psychiatrist	13	0	21	0	34
Pulmonologist	1	6	4	2	13
Surgeon	1	0	6	0	7
Urologist	0	1	2	1	4
Total	**36**	**34**	**140**	**106**	**316**

ISSN: 2789-1895 online
ISSN: 2958-3101 print

Table 5: The classification of DDIs according to the number of drug prescriptions

Number of drugs	Major	Minor	Moderate	Unknown	Total	Percentage of interactions
3	**18**	16	**45**	67	146	**46.2**
4	**11**	12	**51**	35	109	**34.49**
5	2	2	10	1	15	**4.7**
6	1	2	12	2	17	**5.37**
7	0	0	3	0	3	**0.95**
8	4	2	16	1	23	**7.28**
9	0	0	3	0	3	**0.95**
Total	36	34	140	106	316	**100**

Discussion

In this study, there is a difference between the sources of information and data by the sources, where 200 prescriptions were dispensed with 316 DDIs representing 34.4% and 66.0% in BNF and Drugs.com, respectively. Additionally, there are differences of information between the sources, because online Drugs.com may be more advanced and more flexible than BNF printed form, that is why, they investigated the DDIs of variables by Drugs.com source. Most of the DDIs at the moderate class (44.3%) according to Drugs.com, but in BNF, most of the known DDIs at the moderate class (19.6%). Thus, it is important to make people aware to avoid any risk and severity of the DDI. Residential areas, it is collected these prescriptions from two different areas according to the economics of the patients (patient adherence), where Almenshia Pharmacy (high-income area) has 51.9% DDIs, and most of them in the moderate class (25.3%). While Khalifa Pharmacy (low-income area) has 48.1%, most of them at the moderate class (19.0%), because there is no vast difference with the unknown class (19.3%). Depending on the connection, there is a positive correlation between these areas and the number of drugs without significance. These outcomes also explain a small difference between these two areas, and their relationships with patient economics, where, the high-income area has more dispensed drugs number, and better adherence in picking the medications by the patients than the low-income area. Hence, as health care providers, pharmacists have to be aware when dispensing prescriptions, especially in highly economical areas. In a state of gender, there is a difference between gender and the number of drugs, the males have drugs prescribed more than the females leading to a high DDI, the male has 33.6% of known DDIs, and most of them at the moderate class (24.4%), while the female subject has 32.5% of known DDIs and most of them at the moderate class (19.5%). In the case of correlation data between age and the number of drugs prescribed, there is a positive correlation between them. The old adult patients aged above 45 have 56.0% of all DDIs more than other age groups, since most of the patients were old adults. This can explain the highest percentage of this group, but it does not prevent seeking solutions for all age groups to avoid DDIs, especially for old adults, who have health problems. There is the relation between physician specialists and the number of drugs prescribed because they mostly prescribe the drugs depending on the patient's needs. However, as we observed, the orthopedic physicians have DDIs more than other specialists with 56 DDIs and most of them in the moderate class, and the second was psychiatrists have 34 DDIs and most of them in the moderate class. According to the number of drugs, most prescriptions have a minimum of three drugs,

ISSN: 2789-1895 online
ISSN: 2958-3101 print

therefore, the highest percentage of DDIs was 46.2% referred to prescriptions that contained three drugs, and most of them at a moderate class with 45 DDIs and major class, then prescriptions which contain four drugs (34.5% DDIs), and most of them at moderate class. Thus, even with a low number of drugs, DDIs can occur. So, in the answers to the interview questionnaire, there are no strategies to indicate DDIs of prescriptions before dispensing in the two areas, according to their answers, they mostly depend on their knowledge, some other sources such as BNF, or reading the leaflets of medications before dispensing. Regarding DDI, all the detected drugs, that have DDI, are dispensed. All the prescriptions have been dispensed. If the pharmacists reject the prescriptions that indicate other reasons such as the drugs are not available, or the prescriptions are not legal or clear, hence, rejection of the prescription account for other reasons than the existence of DDI. Regarding age, gender, prescriber specialty, and prescription size are randomly selected. However, a larger sample size from different regions of Libya is required to confirm the parameters related to DDIs. This could solve the difference in detected DDIs by using two sources of analysis used in this study.

Conclusion: More than half of the prescribed drug combinations have DDIs (classified as moderate DDIs), and all of them are released for use by the pharmacist. This fact necessitates the following: provision of an accurate DDI checker, it has to be on a desktop for clinical pharmacists/community pharmacists who is to be familiar with such DDI before dispensing prescriptions. The pharmacist has to stop dispensing the prescriptions if contain DDIs, and he/she should communicate continually with the physician, who prescribed the drugs, to alert and attenuate the severity of these risks.

Acknowledgments: The authors would like to thank all the participants who took part in this study.
Author contribution: JRK & SMA designed the study, collected the data and performed data analysis. FNR collected and performed data analysis. JRK interpreted of data & drafted and revised the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for its contents.
Conflict of interest: The authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Ethical issues: Including plagiarism, informed consent, data fabrication or falsification, and double publication or submission were completely observed by the authors.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author declarations: The authors confirm that all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals were obtained.

References

1. Rowland M (2008) Introducing pharmacokinetic and pharmacodynamic concepts. In: Rodrigues D (ed.) Drug-drug interactions. 2nd ed., New York: Informa Healthcare USA. eBook ISBN: 9780429131967.
2. Rekic D, Reynolds KS, Zhao P, Zhang L, Yoshida K, Sachar M, Miller MP, Huang MP, Huang SM, Zineh I (2017) Clinical drug-drug interaction evaluations to inform drug use and enable drug access. Journal of Pharmaceutical Sciences. 106 (9): 2214-2218. doi: 10.1016/j.xphs.2017.04.016
3. Sjöqvist F, Böttiger Y (2010) Historical perspectives: drug interactions - it all began with cheese. Journal of Internal Medicine. 268 (6): 512-515. doi: 10.1111/j.1365-2796.2010.02300.x
4. Cascorbi I (2012) Drug interactions-principles, examples and clinical consequences. Deutsches Arzteblatt International. 109 (33-34): 546-556. doi: 10.3238/arztebl.2012.0546
5. Saverno KR, Hines LE, Warholak TL, Grizzle AJ, Babits L, Clark C, Taylor AM, Malone DC (2011) Ability of pharmacy clinical decision-support software to alert users about clinically important drug-drug interactions. Journal of the American Medical Informatics Association. 18 (1): 32-37. doi: 10.1136/jamia.2010.007609

ISSN: 2789-1895 online
ISSN: 2958-3101 print

6. Lalagkas PN, Poulentzas G, Tsiolis L, Berberoglou E, Litina DH, Douros A, Kontogiorgis C, Constantinides T (2022) Investigating potential drug-drug interactions from Greek e-prescription data. Current Drug Safety. 17 (2): 114-120. doi: 10.2174/1574886316666210816115811
7. Kheshti R, Aalipour M, Namazi S (2016) A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness. Journal of Research in Pharmacy Practice. 5 (4): 257-263. doi: 10.4103/2279-042X.192461
8. Kallio S, Eskola T, Airaksinen M, Pohjanoksa-Mäntylä M (2021) Identifying gaps in community pharmacists' competence in medication risk management in routine dispensing. Innovations in Pharmacy. 12 (1): doi: 10.24926/iip.v12i1.3510
9. Drug interactions checker (2023) Drug Interaction Online. Available at: http://www.drugs.com/drug_interactions.php (Accessed: September 2023).
10. Joint Formulary Committee (2022) British National Formulary. London: BMJ and Royal Pharmaceutical Society, UK.
11. Tragni E, Casula M, Pieri V, Favato G, Marcobelli A, Trotta MG, Catapano AL (2013) Prevalence of the prescription of potentially interacting drugs. PLoS ONE. 8 (10): e78827. doi: 10.1371/journal.pone.0078827
12. Hamadouk R, Albashair ED, Mohammed FM, Yousef BA (2022) The practice of the community pharmacists in managing potential drug-drug interactions: a simulated patient visits. Integrated Pharmacy Research and Practice. 11: 71-84. doi: 10.2147/IPRP.S355675
13. Strandell J, Bate A, Lindquist M, Edwards R (2008) Drug-drug interactions - a preventable patient safety issue? British Journal of Clinical Pharmacology. 65 (1): 144-146. doi: 10.1111/j.1365-2125.2007.02981.x
14. Ansari J (2010) Drug interaction and pharmacist. Journal of Young Pharmacists. 2 (3): 326-331. doi: 10.4103/0975-1483.66807
15. Mousavi S, Norouzi M, Ashouri A, Javadi MR, Gholami K, Hadjibabaie M (2014) Study of potential drug-drug interactions in prescriptions of university-based pharmacies. Journal of Pharmaceutical Care. 2 (2): 60-65. ID: emr-153306.
16. Ahmadizar F, Soleymani F, Abdollahim M (2011) Study of drug-drug interactions in prescriptions of general practitioners and specialists in Iran 2007-2009. Iranian Journal of Pharmaceutical Research. 10 (4): 921-931. PMC: 3813067.
17. Al Ameri1 MN, Makramalla E, Albur U, Kumar A, Rao P (2014) Prevalence of poly-pharmacy in the elderly: implications of age, gender, co-morbidities and drug interactions. SOJ Pharmacy & Pharmaceutical Sciences. 1 (3): 1-7. doi: 10.15223/2374-6866/1/3/00115
18. Elliott R, Shinogle J, Peele P, Bhosle M, Hughes DA (2008) Understanding medication compliance and persistence from an economics perspective. Value in Health. 11 (4): 600-610. doi: 10.1111/j.1524-4733.2007.00304.x
19. Prajapati J, Patel A, Raninga P (2014) Facial age group classification. IOSR Journal of Electronic and Communication Engineering. 9 (1): 33-39. doi: 10.9790/2834-09123339