International Scholars Journals

International Journal of Pharmacy and Pharmacology ISSN 2326-7267 Vol. 13 (10), pp. 001-007, October, 2024. Available online at www.internationalscholarsjournals.org © International Scholars Journals



*Full Length Research Paper*

# Factors Influencing Potential Drug-Drug Interactions in Pulmonology Patients: Age, Hospital Stay, and Polypharmacy

**Mohammad Ismail[1], Zafar Iqbal[1]*, Muhammad Bilal Khattak[2], Arshad Javaid[3] and Tahir Mehmood Khan[4]**

[1]Department of Pharmacy, University of Peshawar, Peshawar, KPK, Pakistan.
[2]Ayub Teaching Hospital (ATH), Abbottabad, KPK, Pakistan.
[3]Post Graduate Medical Institute (PGMI), Lady Reading Hospital (LRH), Peshawar, KPK, Pakistan.
[4]College of Clinical Pharmacy, King Faisal University, Al-Ahsa, Kingdom of Saudi Arabia.

Accepted 22 July, 2024

**The objective of the study was to identify prevalence, types and predictors of potential drug-drug interactions (pDDIs) in pulmonology ward and to report common interactions. Medical records of 400 randomly-selected patients were reviewed for pDDIs using Micromedex Drug-Reax software. Logistic-regression was applied to determine predictors of pDDIs. We identified 126 interacting-combinations that encountered in total 558 pDDIs with median number of 01 pDDI per patient. Overall 45% patients had at least one pDDI; 24.25% were having at least one major pDDI, and 36% patients had at least one moderate pDDI. Among 558 identified pDDIs, most were of moderate (53.6%) or major severity (34%); good (74.2%) or fair (16.3%) type of scientific-evidence; and delayed onset (70%). Top 15 common pDDIs included 6 major, 7 moderate and 2 minor interactions. There was significant association of the occurrence of pDDIs with patient with age of 60 years or more (p <0.001), hospital stay of 7 days or longer (p = 0.01) and taking 7 or more drugs (p <0.001). We have recorded a high prevalence of pDDIs in pulmonology ward, most of which were of moderate severity. Patients with old age, long hospital stay and increased number of drugs were more exposed to pDDIs.**

**Key words:** Drug-drug interactions, potential drug-drug interaction, prescriptions screening, drug related problems, clinical pharmacy.

## INTRODUCTION

The term drug-drug interactions (DDIs) refer to alteration in the pharmacokinetics or effects of a drug by the presence of another drug (Baxter, 2010). It can lead to increased toxicity and untoward effects of many drugs e.g., concomitant use of acetaminophen with isoniazid is associated with higher risk of liver toxicity (Nolan et al., 1994). On the other hand, DDIs can affect therapeutic response as well e.g., rifampin reduces antimicrobial effect of clarithromycin (Yamamoto et al., 2004). Studies have demonstrated that old age, taking increased number of medications, long hospital stay, gender and comorbid conditions are common predictors of DDIs (Doubova et al., 2007; Gagne et al., 2008; Johnell and Klarin, 2007; Juurlink et al., 2003; Katona, 2001; Nobili et al., 2009; Riechelmann et al., 2005).

In hospitalized patients, the issue of DDIs needs more attention due to severity of disease, comorbid conditions, chronic diseases, polypharmacy, complex therapeutic regime, and frequent modification in therapy (Zwart-van Rijkom et al., 2009). Krahenbuhl-Melcher et al. (2007) reported that during hospitalization, 17% of all adverse drug events are caused by DDIs.

The potential clinical consequences of DDIs are predictable; therefore they are mainly considered preventable problems (Juurlink et al., 2003). Studies that explore occurrence and clinical importance of pDDIs will

*Corresponding author. E-mail: zafar_iqbal@upesh.edu.pk. Tel: +92-91-9216750. Fax: +92-91-9218131.

help physicians and clinical pharmacists to identify and prevent these interactions. Substantial numbers of studies have been conducted on drug interactions in internal medicine wards (Egger et al., 2003; Fokter et al., 2010; Glintborg et al., 2005; Vonbach et al., 2008). To the best of our knowledge, no pharmacoepidemiological data are available regarding the evaluation of pDDIs in pulmonology wards. Therefore, the aim of our study was to identify prevalence, types and predictors of pDDIs in pulmonology ward. A second aim was to report commonly occurring interacting drug-combinations in pulmonology ward.

## METHODS

### Study design and approval

This cross-sectional study was carried out using medical charts of 400 randomly-selected patients who had been admitted to pulmonology ward of the hospital during a 1-year period from 1st September 2008 to 31st August 2009. This study was approved by the Ethical Committee of the Department of Pharmacy, University of Peshawar.

### Setting

We conducted this study in pulmonology ward of Ayub Teaching Hospital (ATH), Abbottabad, KPK, Pakistan. ATH is a 1000-bed tertiary care teaching hospital that provides health care and referral services to a population of more than 400,000 inhabitants of Abbottabad and many Northern Areas of Pakistan including Mansehra, Kohistan and Azad Jammu and Kashmir. In ATH, there are general medical, general surgical and obstetrics/gynaecology wards (three each); paediatrics, ENT and ophthalmology wards (two each); pulmonology, psychiatry, dermatology, gastroenterology, urology, orthopaedic, cardiothoracic, oncology and endocrinology ward (one each), and an accident and emergency department.

### Sample size

We used the following formula for the estimation of sample size:

$$n = z^2 p(1-p) / d^2$$

where *n* is sample size, *Z* is Z-statistic for a level of confidence, *P* is anticipated prevalence or proportion and *d* is margin of error (Wild and Seber, 1999).

In the aforementioned formula, we used anticipated prevalence of 50%; 5% margin of error; and 95% confidence level. A minimum sample size of 384 was obtained. For our study, we considered it equivalent to 400. This sample was randomly taken from a 1-year period data (from 1st September 2008 to 31st August 2009), during which total 1700 patients were admitted to ward.

### Data collection and screening of pDDIs

Permission was obtained from hospital administration to conduct this study in pulmonology ward. Medical charts were screened for pDDIs using drug interaction software, Micromedex Drug-Reax® System (Anonymous, 2011). During screening, we considered all prescribed medications used by the patients in hospital, that is, from the time of admission till discharge and that included all regular and PRN (pro re nata: as required) medications. PDDIs were classified into different types as follows.

#### *Onset*

**Rapid:** The effect of interaction will occur within 24 h of administration.

**Delayed:** The effect will occur if the interacting combination is administered for more that 24 h, that is, days to week(s).

#### *Severity*

**Contraindicated:** The drug-combination is contraindicated for concurrent use.

**Major:** If there is risk of death and/or medical intervention is required to prevent or minimize serious negative outcome.

**Moderate:** The effect of interaction can deteriorate patient's condition and may require alteration of therapy.

**Minor:** Little effects are produced that do not impair therapeutic outcome and there is no need of any major change in therapy.

#### *Scientific evidence (Documentation)*

**Excellent:** The interaction has been clearly demonstrated in well-controlled studies.

**Good:** Studies strongly suggest that the interaction exists except proof of well-controlled studies.

**Fair:** Available evidences are poor, but clinicians suspect the interaction on the basis of pharmacologic considerations, or, evidences are good for an interaction of pharmacologically similar drug.

**Poor:** Theoretically the interaction may occur but reports are very limited, such as few case reports.

**Unlikely:** Data are very poor and lack a proper pharmacologic basis.

### Statistical analyses

Results are presented as median, ranges and proportions, where appropriate. We used logistic regression to calculate the odds ratio for specific risk factors including age, gender, hospital stay and number of drugs. Exposure to pDDI(s) was the dependent variable in the model (0 = absent, 1 = present). The following variables were included in the model as predictors of pDDIs: patient's age (1 = below 60 years; 2 = 60 years or older), gender (1 = female; 2 = male), hospital stay (1 = less than 7 days; 2 = 7 days or above), and number of drugs (1 = less than 7; 2 = 7 or above). We used "Enter" method for analysis. The Hosmer–Lemeshow test was used to check goodness-of-fit of the model. P-value of 0.05 or less was considered statistically significant. SPSS for Windows version 16 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses.

**Table 1.** General patient characteristics.

| **Gender** | **Patients: *n* (%)** |
|---|---|
| Male | 176 (44) |
| Female | 224 (56) |
| | |
| **Age (years)** | **Patients: *n* (%)** |
| ≤14 | 11 (2.75) |
| 15-30 | 63 (15.75) |
| 31-45 | 75 (18.75) |
| 46-59 | 68 (17) |
| ≥60 | 183 (45.75) |
| | |
| | **Years** |
| Median | 55 |
| Range | 2-100 |
| | |
| **Hospital stay (days)** | **Patients: *n* (%)** |
| ≤3 | 133 (33.25) |
| 4-6 | 164 (41) |
| ≥7 | 103 (25.75) |
| | |
| | **Days** |
| Median | 5 |
| Range | 1-22 |
| | |
| **Prescribed medications per patient** | **Patients: *n* (%)** |
| <4 | 52 (13) |
| 5-6 | 132 (33) |
| ≥7 | 216 (54) |
| | |
| | **Drugs** |
| Median | 7 |
| Range | 1-19 |

## RESULTS

### General patient characteristics

Of the total 400 patients, 176 (44%) were male and 224 (56%) were female; median age was 55 years; median hospital stay was 5 days and median number of prescribed medications was 7 (Table 1).

### Prevalence of pDDIs

In our study, we identified total 558 numbers of pDDIs and 126 types of interacting combinations. Overall, 180 (45%) patients had at least one pDDI regardless of type of severity; 97 (24.25%) and 144 (36%) patients were having at least one pDDI of major and moderate severity, respectively (Table 2). Minor and contraindicated types of pDDIs were least prevalent. In majority cases 1 to 2 pDDIs per patients were identified with median of 01 pDDI.

### Types of pDDIs

The identified pDDIs were classified on the basis of level of onset, severity and scientific evidence. Table 3 shows these types for 558 numbers of pDDIs. Among 558 pDDIs, most were of moderate (299, 53.6%) or major severity (190, 34%); good (414, 74.2%) or fair (91, 16.3%) type of scientific evidence; and delayed onset (390, 70%).

### Common interacting drug-combinations

We identified a total 126 types of interacting drug-combinations. Common combinations of major, moderate

**Table 2.** Prevalence of potential drug-drug interactions (pDDIs).

| Types of pDDIs | Patients: n (%) |
|---|---|
| Overall* | 180 (45) |
| Contraindicated | 6 (01) |
| Major | 97 (24.25) |
| Moderate | 144 (36) |
| Minor | 49 (12.25) |
| **Number of pDDIs per patient** | **Patients: n (%)** |
| 1-2 | 95 (23.75) |
| 3-5 | 55 (13.75) |
| ≥6 | 30 (7.5) |
| | **PDDIs (n = 558)** |
| Median | 01 |
| Range | 1-9 |

* Overall prevalence means presence of at least one pDDIs regardless of severity-type.

**Table 3.** Levels of the identified potential drug-drug interactions (pDDIs).

| Level | Frequency (in 558 pDDIs) n (%) |
|---|---|
| **Severity** | |
| Contraindicated | 6 (01) |
| Major | 190 (34) |
| Moderate | 299 (53.6) |
| Minor | 63 (11.3) |
| **Documentation** | |
| Excellent | 53 (9.5) |
| Good | 414 (74.2) |
| Fair | 91 (16.3) |
| **Onset** | |
| Rapid | 168 (30) |
| Delayed | 390 (70) |

and minor severities along with their frequencies are shown in Table 4. Top 15 frequently occurring pDDIs included 6 major, 7 moderate and 2 minor types of pDDIs.

### Predictors of pDDIs

In logistic regression analysis (Table 5), there was significant association of the occurrence of pDDIs with patient age of 60 years or more (p = <0.001), hospital stay of 7 days or longer (p = 0.01) and taking 7 or more drugs (p = <0.001).

## DISCUSSION

Overall prevalence of pDDIs in our study was 45%. In other studies a prevalence rate of 27.8% in hospitalized patients (Zwart-van Rijkom et al., 2009); 51 to 60% in interanal medicine wards (Egger et al., 2003; Fokter et al., 2010) and 63% in oncology wards (Riechelmann et al., 2005) have been reported. In our study, prevalence of pDDIs of major severity was 27.2%. Fokter et al. (2010) reported pDDIs of major severity in 13% patients and Egger et al. (2003) in 12.2% patients. We recorded average 1.4 and median number of 01 pDDI per patient in our study. Average 1.44 pDDIs per patient and median pDDIs of 2 per patient have been reported by other studies. (Egger et al., 2003; Fokter et al., 2010). This comparison indicates that pDDIs in pulmonology ward are as imporatant as in other wards.

All pDDIs are not equally harmful. Therefore, different drug interactions compendia classify drug interactions on the basis of severity, onset, evidences in scientific literature and management options (Anonymous, 2011; Hansten and Horn, 2008; Tatro, 2009). Identification of levels for each pDDI is very helpful in assessing its potential clinical importance and for appropriate management. For this purpose, we categorized all identified pDDIs into different types (Table 3). Our findings regarding these types of pDDIs are consistent with many other studies (Cruciol-Souza and Thomson, 2006; Egger et al., 2003; Fokter et al., 2010; Riechelmann et al., 2005). In our study, the “Major” and “Moderate” severity and “Good” scientific evidence, identified for majority of pDDIs are of special concern. These findings suggest that the identified pDDIs have high potential to deteriorate patients’ clinical condition or to alter therapeutic response. We recommend careful monitoring in order to avoid the negative outcomes of these pDDIs.

Common interacting drug-combinations of major and moderate severity are very important for practitioners because these pDDIs are more likely to produce negative outcomes (Table 4). Concurrent use of isoniazid and rifampin is associated with higher risk of hepatotoxicity than with either agent alone. Use of this combination is common and therapeutically valuable. Caution is required in patients with hepatic impairment, malnourished patients, the elderly, and children under 2 years of age. Patients should be monitored for clinical symptoms of liver toxicity including fever, anorexia, vomiting and jaundice (Baxter, 2010; Yew and Leung, 2006). According to CDC (Centers for Disease Control and Prevention) update and some other reports, combination of rifampin with pyrazinamide may result in severe hepatic injury. Extreme caution is advised in case of high

**Table 4.** Common interacting drug-combinations.

| Interaction | Frequency |
|---|---|
| **Contraindicated interactions** | |
| Thioridazine + fluoroquinolones (levofloxacin or sparfiloxacin) | 5 |
| **Major interactions** | |
| Isoniazid + rifampin; rifampin + pyrazinamide | 38 each |
| Spironolactone + captopril | 18 |
| Potassium chloride + spironolactone | 15 |
| Potassium chloride + captopril | 13 |
| Digoxin + spironolactone | 10 |
| Clopidogrel + aspirin | 8 |
| Clopidogrel + esomeprazole; clopidogrel + omeprazole; gentamicin + furosemide | 4 each |
| Heparin + aspirin; heparin + nitroglycerin | 3 each |
| **Moderate interactions** | |
| Dexamethasone + rifampin | 41 |
| Furosemide + captopril | 38 |
| Acetaminophen + isoniazid | 20 |
| Digoxin + furosemide | 16 |
| Prednisolone + rifampin | 15 |
| Furosemide + aspirin | 13 |
| Levofloxacin + prednisolone | 12 |
| Aminophylline + rifampin | 9 |
| Aspirin + dexamethasone; nitroglycerin + aspirin | 8 each |
| Alprazolam + theophylline; captopril + aspirin; clarithromycin + rifampin | 7 each |
| **Minor interactions** | |
| Aminophylline + furosemide | 14 |
| Theophylline + furosemide | 11 |
| Isoniazid + prednisolone | 7 |
| Aminophylline + clarithromycin; aminophylline + ranitidine; theophylline + ranitidine | 5 each |

**Table 5.** Logistic regression analysis*.

| Variable | Patients: *n* (%) | | OR** (95% CI**) | P-value |
|---|---|---|---|---|
| | Interaction present (*n* = 180 ) | Interaction absent (*n* = 220 ) | | |
| **Patient age (years)** | | | | |
| < 60 | 65 | 152 | 3.85 (2.16-6.84) | <0.001 |
| ≥ 60 | 115 | 68 | | |
| **Gender** | | | | |
| Female | 78 | 98 | 0.99 (0.56-1.76) | 0.99 |
| Male | 102 | 122 | | |
| **Hospital stay (days)** | | | | |
| < 7 | 104 | 193 | 2.33 (1.22-4.44) | 0.01 |
| ≥ 7 | 76 | 27 | | |
| **Number of drugs** | | | | |

**Table 5.** Contd.

| | | | | |
|---|---|---|---|---|
| < 7 | 16 | 168 | 27.62 (14.57-52.37) | <0.001 |
| ≥ 7 | 164 | 52 | | |

*Hosmer–Lemeshow goodness-of-fit test: P = 0.6; ** OR: Odds ratio; CI: Confidence interval.

risk situations e.g., use of other hepatotoxic drugs, underlying liver disease, use of excessive alcohol and history of isoniazid-induced hapatoxicity. Liver function tests should be monitored throughout the use of this combination (Anonymous, 2003; Kunimoto et al., 2003; McNeill et al., 2003). Combination of spironolactone with captopril may result in hyperkalemia. Although such increase is usually transient, it is of special concern in patients with renal impairment or diabetes, those with a risk for dehydration, and in the elderly. In such situations, the hyperkalemia associated with this combination may lead to severe arrhythmias and death. It is suggested to monitor the patient and to limit the dose of spironolactone to 25 mg daily or on alternate day (Wrenger et al., 2003). Concurrent use of potassium chloride with spironolactone can lead to severe and even life-threatening hyperkalemia. Common manifestations of hyperkalemia include muscular weakness, paraesthesia, flaccid paralysis of the extremities, fatigue, bradycardia, electrocardiogram (ECG) abnormalities and shock. Potassium chloride and other potassium supplements are better to avoid during spironolactone-use, otherwise close monitoring of serum-potassium level is required (Baxter, 2010; Greenblatt and Koch-Weser, 1973). Concurrent use of potassium chloride with captopril can cause severe hyperkalemia that may lead to death especially in renally impaired and elderly patients. Patients should be monitored and should be advised to restrict excessive potassium use (Anonymous, 2011; Ray et al., 1999). Rifampin can reduce the pharmacological effects of corticosteroids (dexamethasone and prednisolone). It is suggested to monitor corticosteroid effects and increase the dose if necessary. A dose reduction may be necessary if rifampin is discontinued (Carrie et al., 1994; Gupta et al., 1995). The combination of captopril with furosemide is normally safe and effective, but first-dose hypotension can occur that is manifested by dizziness, lightheadedness, fainting. Such effects are more likely if the dose of diuretic is high or if there is some predisposing conditions. This is a well established interaction therefore dose adjustment and monitoring is suggested (Baxter, 2010; Mclay et al., 1993). Concomitant use of acetaminophen with isoniazid can lead to increased risk of liver toxicity. Usual analgesic doses of acetaminophen (4 g per day) may not be safe in some individuals, therefore its use should be limited in patients taking isoniazid (Nolan et al., 1994). Furosemide causes hypokalemia that increases digoxin toxicity (nausea, vomiting, cardiac arrhythmias). Serum-potassium should be monitored and patient should be educated to maintain adequate intake of dietary potassium and/or potassium supplements (Steiness and Olesen, 1976). Concurrent use of furosemide and aspirin may result in reduction of the diuretic effect of furosemide. This combination may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration. Moreover, the risk of aspirin-induced ototoxicity (high dose effect) would be greater if given with other ototoxic drugs like furosemide. Patients should be monitored for therapeutic and toxic effects; and high dose aspirin should be avoided if given in combination with furosemide (Bartoli et al., 1980; Yorgason et al., 2006). The practitioners should monitor the patients carefully for all potential clinical consequences of these interactions to manage them accordingly.

Our findings regarding significant association of pDDIs with old age, long hospital stay and taking increased number of drugs are consistent with other studies (Doubova et al., 2007; Gagne et al., 2008; Johnell and Klarin, 2007; Riechelmann et al., 2005). These predictors of pDDIs should be considered in clinical practice to prevent negative clinical consequences of interactions.

## Conclusions

In our study, we have recorded a high prevalence of pDDIs in pulmonology ward, most of which were of moderate severity. Patients with old age, long hospital stay and increased number of drugs were more exposed to pDDIs. We recommend careful monitoring in order to avoid the negative outcomes of these pDDIs.

## ACKNOWLEDGEMENTS

We are very thankful to University of Peshawar for financial support. We are grateful to Consultant and all other Staff of Pulmonology Ward of Ayub Teaching Hospital, for administrative support and Mr. Muhammad Imran Khan and Mr. Jibran Hasan Khan, Ayub Medical College, Abbottabad, for assistance in data collection.

### REFERENCES

Anonymous (2003). Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use

of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection---United States, 2003. Morbidity and Mortality Weekly Report, 52: 735-739.
Anonymous (2011). MICROMEDEX DRUG-REAX® System [database on CD-ROM]. Volume 148. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc.

Bartoli E, Arras S, Faedda R, Soggia G, Satta A, Olmeo NA (1980). Blunting of furosemide diuresis by aspirin in man. J. Clin. Pharmacol., 20: 452-458.
Baxter K (2010). Stockley's Drug Interactions. London, Chicago, Pharmaceutical Press.
Carrie F, Roblot P, Bouquet S, Delon A, Roblot F, Becq-Giraudon B (1994). Rifampin-induced nonresponsiveness of giant cell arteritis to prednisone treatment. Arch. Int. Med., 154: 1521-1524.
Cruciol-Souza J, Thomson J (2006). A pharmacoepidemiologic study of drug interactions in a Brazilian teaching hospital. Clinics, 61: 515-520.

Doubova SV, Reyes-Morales H, Torres-Arreola LDP, Suarez-Ortega M (2007). Potential drug-drug and drug-disease interactions in prescriptions for ambulatory patients over 50 years of age in family medicine clinics in Mexico City. BMC Health Serv. Res., 7: 147.
Egger SS, Drewe J, Schlienger RG (2003). Potential drug-drug interactions in the medication of medical patients at hospital discharge. Eur. J. Clin. Pharmacol., 58: 773-778.
Fokter N, Mozina M, Brvar M (2010). Potential drug-drug interactions and admissions due to drug-drug interactions in patients treated in medical departments. Wien Klin Wochenschr, 122: 81-88.
Gagne JJ, Maio V, Rabinowitz C (2008). Prevalence and predictors of potential drug-drug interactions in Regione Emilia-Romagna, Italy. J. Clin. Pharm. Ther., 33: 141-151.
Glintborg B, Andersen S, Dalhoff K (2005). Drug-drug interactions among recently hospitalised patients – frequent but mostly clinically insignificant. Eur. J. Clin. Pharmacol., 61: 675-681.
Greenblatt DJ, Koch-Weser J (1973). Adverse reactions to spironolactone. A report from the Boston Collaborative Drug Surveillance Program. JAMA, 225: 40-43.
Gupta D, Yadav S, Behera D, Jindal SK (1995). Worsening of steroid dependent asthma : A possible role of rifampicin. Indian J. Chest Dis. Allied Sci., 37: 35-38.
Hansten PD, Horn JR (2008). Drug Interactions Analysis and Management, Wolters Kluwer Health, Inc. St. Louis, MO.
Johnell K, Klarin I (2007). The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. Drug Saf., 30: 911-918.
Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA (2003). Drug-Drug Interactions Among Elderly Patients Hospitalized for Drug Toxicity. JAMA, 289: 1652-1658.
Katona CLE (2001). Psychotropics and drug interactions in the elderly patient. Int. J. Geriatr. Psychiatry, 16: S86-S90.
Krahenbuhl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krahenbuhl S (2007). Drug-related problems in hospitals: a review of the recent literature. Drug Saf., 30: 379-407.
Kunimoto D, Warman A, Beckon A, Doering D, Melenka L (2003). Severe hepatotoxicity associated with rifampin-pyrazinamide preventative therapy requiring transplantation in an individual at low risk for hepatotoxicity. Clin. Infect Dis., 36: E158-E161.
Mclay JS, Mcmurray JJ, Bridges AB, Fraser CG, Struthers AD (1993). Acute Effects of Captopril on the Renal Actions of Furosemide in Patients with Chronic Heart-Failure. Am. Heart J., 126: 879-886.
McNeill L, Allen M, Estrada C, Cook P (2003). Pyrazinamide and rifampin vs isoniazid for the treatment of latent tuberculosis: improved completion rates but more hepatotoxicity. Chest, 123: 102-106.
Nobili A, Pasina L, Tettamanti M, Lucca U, Riva E, Marzona I, Monesi L, Cucchiani R, Bortolotti A, Fortino I (2009). Potentially severe drug interactions in elderly outpatients: results of an observational study of an administrative prescription database. J. Clin. Pharm. Ther., 34: 377-386.
Nolan CM, Sandblom RE, Thummel KE, Slattery JT, Nelson SD (1994). Hepatotoxicity associated with acetaminophen usage in patients receiving multiple drug therapy for tuberculosis. Chest, 105: 408-411.
Ray K, Dorman S, Watson R (1999). Severe hyperkalaemia due to the concomitant use of salt substitutes and ACE inhibitors in hypertension: a potentially life threatening interaction. J. Hum. Hypertens, 13: 717-720.
Riechelmann RP, Moreira F, Smaletz Ò, Saad ED (2005). Potential for drug interactions in hospitalized cancer patients. Cancer Chemother Pharmacol., 56: 286-290.
Steiness E, Olesen KH (1976). Cardiac arrhythmias induced by hypokalaemia and potassium loss during maintenance digoxin therapy. Br. Heart J., 38: 167-172.
Tatro D (2009). Drug Interaction Facts, Facts and Comparisons. Wolters Kluwer Health, St. Louis, Missouri.
Vonbach P, Dubied A, Krähenbühl S, Beer JH (2008). Prevalence of drug-drug interactions at hospital entry and during hospital stay of patients in internal medicine. Eur. J. Int. Med., 19: 413-420.
Wild CJ, Seber GAF (1999). Chance Encounter: A First Course in Data Analysis and Inference, Wiley, New York.
Wrenger E, Muller R, Moesenthin M, Welte T, Frolich JC, Neumann KH (2003). Interaction of spironolactone with ACE inhibitors or angiotensin receptor blockers: analysis of 44 cases. BMJ, 327: 147-149.
Yamamoto F, Harada S, Mitsuyama T, Harada Y, Kitahara Y, Yoshida M, Nakanishi Y (2004). Concentration of clarithromycin and 14-R-hydroxy-clarithromycin in plasma of patients with Mycobacterium avium complex infection, before and after the addition of rifampicin. Jpn J. Antibiot., 57: 124-133.
Yew WW, Leung CC (2006). Antituberculosis drugs and hepatotoxicity. Respirology, 11: 699-707.
Yorgason JG, Fayad JN, Kalinec F (2006). Understanding drug ototoxicity: molecular insights for prevention and clinical management. Expert Opin. Drug Saf., 5: 383-399.
Zwart-van Rijkom JEF, Uijtendaal EV, Ten Berg MJ, Van Solinge WW, Egberts ACG (2009). Frequency and nature of drug–drug interactions in a Dutch university hospital. Br. J. Clin. Pharmacol., 68: 187-193.