Tropical Journal of Pharmaceutical Research April 2012; 11 (2): 289-296

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v11i2.17

Research Article

Potential Drug-Drug Interactions in Psychiatric Ward of a Tertiary Care Hospital: Prevalence, Levels and Association with Risk Factors

Mohammad Ismail[1], Zafar Iqbal[1*], Muhammad Bilal Khattak[2], Arshad Javaid[3], Muhammad Imran Khan[4], Tahir Mehmood Khan[5] and Syed Muhammad Asim[6]

[1] Department of Pharmacy, University of Peshawar, Peshawar, [2]Ayub Teaching Hospital (ATH), Abbottabad, [3]Post Graduate Medical Institute (PGMI), Lady Reading Hospital (LRH), Peshawar, [4]Ayub Medical College, Abbottabad, KPK, Pakistan, [5]College of Clinical Pharmacy, King Faisal University, Al-Ahsa, Kingdom of Saudi Arabia, [6]Department of Statistics, University of Peshawar, Peshawar, KPK, Pakistan.

Abstract

Purpose: *To identify the prevalence of potential drug-drug interactions (pDDIs) in a psychiatric ward, their levels and association with risk factors.*
Methods: *This study was conducted in the psychiatric ward of Ayub Teaching Hospital, Abbottabad, Pakistan. Medical records of 415 patients were retrospectively reviewed for pDDIs using Micromedex Drug-Reax software. Logistic regression was applied to determine association of pDDIs with age, gender, hospital stay and number of drugs.*
Results: *In our study, we identified total number of 825 pDDIs of 126 types, with median number of 1 pDDIs per patient. Overall 64.8 % of the patients had at least one pDDI; 27.2 % at least one major pDDI; and 58.5 % patients at least one moderate pDDI. Among 825 identified pDDIs, most were of moderate (75.6 %) or major (20.8 %) severity, good (66.4 %) or fair (29 %) type of scientific evidence; and delayed onset (71 %). The most frequent major and moderate pDDIs included haloperidol + procyclidine (127 cases), haloperidol + olanzapine (49), haloperidol + promethazine (47), haloperidol + fluphenazine (41), diazepam + divalproex sodium (40), haloperidol + trihexyphenidyl (37), lorazepam + divalproex sodium (34), fluphenazine + procyclidine (33) and olanzapine + divalproex sodium (32). There was significant association of occurrence of pDDIs with hospital stay of 7 days or longer ($p = 0.005$) and taking 7 or more drugs ($p < 0.001$).*
Conclusion: *A high prevalence of pDDIs in the psychiatric ward was recorded, a majority of which were of moderate severity. Patients with long hospital stay and increased number of drugs were more exposed to pDDIs.*

Keywords: *Drug-drug interactions, Potential drug-drug interaction, Prescriptions screening, Drug-related problems, Clinical pharmacy.*

Received: 12 July 2011 *Revised accepted: 23 February 2012*

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

INTRODUCTION

Drug-drug interactions (DDIs) can lead to alteration of therapeutic response or increase untoward effects of many drugs [1]. The issue of DDIs needs more attention in the case of hospitalized patients due to severity of disease, polypharmacy, co-morbid conditions, chronic diseases, complex therapeutic regime, and frequent modification in therapy [2]. Prevalence of potential DDIs (pDDIs) in hospital settings has been estimated in some recent studies to be in the range of 27.8 to 51.4 % [2-4]. Old age, taking increased number of medications, long hospital stay, gender and comorbid conditions have been reported as common risk factors for DDIs [5-11].

In comparison to other clinical specialty wards, e.g., internal medicine wards [4,12,13], very few studies have addressed the issue of DDIs in psychiatric wards. A small scale cross-sectional survey (n = 48), conducted in elderly psychiatric wards identified a total of 152 pDDIs in 96 % (46/48) of prescriptions [14]. Davies *et al* evaluated 323 prescriptions of adult and elderly patients of psychiatric wards in England for pDDIs involving two isoforms of cytochrome P450, CYP2D6 and CYP3A4. Eighty two CYP2D6-combinations in 62 patients (19 %) and 24 CYP3A4-combinations in 20 patients (6 %) were reported to be clinically important or potentially clinically important [15]. In a similar study (n = 323) conducted in psychiatric wards in England to assess prevalence of PRN (pro re nata, i.e., as required) drug prescriptions and potential for interactions involving CYP2D6 and CYP3A4, it was found that 20 % of the patients were prescribed drug combinations interacting with CYP2D6 or CYP3A4 which included one or more drugs prescribed on a PRN basis [16]. Studies are needed to explore the overall pattern of pDDIs in psychiatric wards along with their levels and correlation with different risk factors.

The primary aim of our study was to identify the prevalence of pDDIs in prescriptions of hospitalized patients in a psychiatric ward in a Pakistani tertiary care hospital, their levels, and association with specific potential risk factors such as age, gender, hospital stay and number of drugs. A secondary aim was to report commonly occurring interacting drug-combinations in the psychiatric ward.

METHODS

Setting

This study was conducted in the psychiatric ward of Ayub Teaching Hospital (ATH), Abbottabad, KPK, Pakistan, which is a 1000-bed tertiary care teaching hospital. ATH provides health care and referral services to a population of more than 400,000 inhabitants in Abbottabad and several northern areas of Pakistan, including Mansehra, Kohistan and Azad Jammu and Kashmir (AJK).

Design and study population

This was a retrospective cross-sectional study carried out using medical records of patients admitted to the psychiatric ward during a 1-year period from 1st September 2008 to 31st August 2009. Patients' records with incomplete information were excluded from the study. This study was approved by the Ethical Committee of the Department of Pharmacy, University of Peshawar.

Data collection

Permission was obtained from hospital administration to use patients' medical records for the collection and analysis of prescription data. The records were retrospectively reviewed and the following data were collected: patient's age, gender, duration of hospital stay, and names and number of prescribed drugs.

Screening of pDDIs

All medications that were prescribed to the patients during the entire hospital stay, i.e., from the date of admission until discharge, and these included routine and PRN medications, were screened for pDDIs. Micromedex Drug-Reax® System (Thomson Reuters Healthcare Inc., Greenwood Village, Colorado, USA) was used to screen and classify pDDIs [17]. PDDIs were categorized into different levels as follows.

Onset

- *Rapid*: The effect of interaction occurs within 24 hours of administration.
- *Delayed*: The effect occurs if the interacting combination is administered for more than 24 h, i.e., days to week(s).

Severity

- *Contraindicated:* The drug-combination is contraindicated for concurrent use.
- *Major:* There is risk of death and/or medical intervention is required to prevent or minimize serious negative outcomes.
- *Moderate:* The effect of interaction can deteriorate patient's condition and may require alteration of therapy.
- *Minor:* Little effects are produced that don't 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 the interaction is suspected 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.

Data analyses

The results are presented as median, range and proportion where appropriate. Logistic regression was applied to determine the odds ratio for different risk factors, i.e., age, gender, hospital stay and number of drugs. The presence of 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 46 years, 2 = ≥ 46 years), gender (1 = female, 2 = male), hospital stay (1 = < 7 days, 2 = ≥ 7 days), and number of drugs (1 = < 7, 2 = ≥ 7). "Enter" method was used for analysis. Hosmer–Lemeshow test was used to evaluate 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.

RESULTS

General patient characteristics

Of the total of 427 patients' medical records, 12 were excluded due to incomplete information, while 415 were reviewed for pDDIs. In the study, among the 415 patients, 195 (47 %) were male and 220 (53 %) female; median age was 25 years; median hospital stay 5 days and median number of prescribed medications 5 (Table 1).

Prevalence of pDDIs

Table 2 shows that 269 (64.8 %) patients had at least one pDDI regardless of type of severity; 113 (27.2 %) and 243 (58.5 %) patients had at least one pDDI of major and moderate severity, respectively. Contra-indications and minor types of pDDIs were least prevalent. In a majority cases, 1 - 2 pDDIs per patients were identified with a median of 1 pDDI. A total number of 825

pDDIs and 126 types of interacting combinations were identified.

Table 1: General patient characteristics

Gender	Patients, *n* (%)
Male	195 (47)
Female	220 (53)
Age (years**)**	
≤ 14	20 (5)
15 - 30	255 (61)
31 - 45	92 (22)
46 - 60	41 (10)
≥ 61	7 (2)
Median	25 yr
Range	8 – 100 yr
Hospital stay (days)	
≤ 3	132 (32)
4 - 6	139 (33)
≥ 7	144 (35)
Median	5 days
Range	1 – 20 days
No. of prescribed medications per patient	
≤ 4	137 (33)
5 - 6	124 (30)
≥ 7	154 (37)
Median	5 drugs
Range	1-14 drugs

Table 2: Prevalence of potential drug-drug interactions (pDDIs)

Prevalence with respect to severity	Patients, n (%)
Overall	269 (64.8)
Contraindicated	4 (01)
Major	113 (27.2)
Moderate	243 (58.5)
Minor	25 (06)
Number of pDDIs per patient	**Patients, n (%)**
1-2	151 (36.4)
3-5	77 (18.6)
≥6	41 (10)
	PDDIs (n = 825)
Median	01
Range	1-10

Levels of pDDIs

The identified pDDIs were categorized into different levels according to onset, severity and scientific evidence. Table 3 shows these levels for all the pDDIs and 126 types of interacting combinations. Among the 825 pDDIs, most were of moderate (624; 75.6 %) or major severity (172; 20.8 %); good (548; 66.4 %) or fair (239; 29 %) type of scientific evidence; and delayed onset (586; 71%). A similar pattern was recorded for the 126 types of interacting combinations (Table 3).

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

Level	Frequency of pDDIs (n = 825) *n (%)*	Frequency of pDDIs type (n = 126) *n (%)*
Severity		
Contraindicated	4 (0.5)	3 (2.4)
Major	172 (20.8)	38 (30.2)
Moderate	624 (75.6)	77 (61.1)
Minor	25 (3)	8 (6.3)
Documentation		
Excellent	38 (4.6)	6 (4.8)
Good	548 (66.4)	87 (69)
Fair	239 (29)	33 (26.2)
Onset		
Rapid	239 (29)	32 (25.4)
Delayed	586 (71)	94 (74.6)

Common interacting combinations

In the study, we identified a total 126 types of interacting combinations. Common combinations along with their frequencies are shown in Table 4. The top 20 commonly occurring pDDIs include 5 major, 14 moderate and 1 minor pDDIs. Haloperidol, procyclidine, fluphenazine, promethazine, olanzapine, trihexyphenidyl, fluoxetine, chlorpromazine, divalproex sodium, diazepam and lorazepam were the drugs most commonly encountered in these pDDIs.

Association with potential risk factors

Table 5 shows that, based on univariate analysis, there was significant association of the occurrence of one or more pDDIs with hospital stay of 7 days or longer ($p < 0.001$) ;

taking 7 or more drugs ($p < 0.001$) and male gender ($p = 0.04$). In multivariate analysis, association was significant only in the case of hospital stay of 7 days or longer ($p = 0.005$) and taking 7 or more drugs ($p < 0.001$).

Table 4: Common interacting drug-combinations

Interaction	Frequency
Contraindicated	
Trifluoperazine + venlafaxine	2
Major	
Haloperidol + promethazine	47
Haloperidol + fluphenazine	41
Haloperidol + chlorpromazine	14
Haloperidol + lithium	8
Propranolol + haloperidol	7
Fluphenazine + lithium	6
Imipramine + haloperidol; Diclofenac sodium + sertraline; Haloperidol + fluoxetine; Ibuprofen + sertraline; Imipramine + fluoxetine; Amitriptylline + haloperidol; Diclofenac sodium + escitalopram; Fluoxetine + trazodone; Imipramine + sertraline; Venlafaxine + tramadol; Venlafaxine + trazodone	≤ 5
Moderate	
Haloperidol + procyclidine	127
Haloperidol + olanzapine	49
Diazepam + divalproex sodium	40
Haloperidol + trihexyphenidyl	37
Lorazepam + divalproex sodium	34
Fluphenazine + procyclidine	33
Olanzapine + divalproex sodium	32
Promethazine + procyclidine	29
Promethazine + trihexyphenidyl	25
Trifluoperazine + procyclidine	17
Alprazolam + fluoxetine; Divalproex sodium + risperidone	13 each
Fluphenazine + trihexyphenidyl	12
Chlorpromazine + trihexyphenidyl	10
Minor	
Diazepam + fluoxetine	13
Clonazepam + omeprazole; Diazepam + omeprazole; Propranolol + ciprofloxacin; Propranolol + fluoxetine	≤ 5

DISCUSSION

The results of our study show that the prevalence of pDDIs in the psychiatric ward (64.8%) was higher compared to other hospitalized patients (49.7 % [3] and 27.8 % [2]) or patients of other wards such as internal medicine wards (51 % [4] and 60 % [13]) and oncology wards (63 % [5]). In our study, prevalence of pDDIs of major severity (27.2 %) was also higher compared to other studies. Vonbach *et al* reported pDDIs of major severity in 3.1 % patients [12] while in another study Cruciol-Souza and Thomson estimated prevalence rate of 3.4 % for pDDIs of major severity [3]. We recorded average 1.98 and median number of 1 pDDI per patient in our study. Average 1.44 pDDIs per patient was reported by Fokter *et al* [4] and median pDDIs of 2 per patient was estimated by Egger *et al* [13]. Vasudev and Harrison demonstrated a high prevalence of pDDIs (96 %) in psychiatric wards [14]; Janchawee *et al* reported the highest prevalence of pDDIs in psychiatric prescriptions (57.8 %) compared to internal medicine (42.4 %), pediatrics (13.1 %) and surgery (23.3 %) [18]. Both of above studies support our results, but partially, because study of Vasudev and Harrison included a small number (n = 48) of elderly patients only while Janchawee *et al* carried out their study on prescriptoin data of outpatient department of a university hospital. We can conclude that prevalence of pDDIs was higher in psychiatric ward as compared to other wards but further studies are needed.

Moreover, this difference in prevalence may also be a result of high utilization of drugs having more interacting potentials (e.g., haloperidol, procyclidine, fluphenazine, promethazine, olanzapine, trihexyphenidyl, diazepam and lorazepam), absence of clinical pharmacist and/or drug information services by specialists (as in the case of the hospital studied), sensitivity of the source used for the screening of drug interactions and methodological design of the study.

Table 5: Logistic regression analysis*

Variable	Patients, *n* (%)		Univariate		Multivariate	
	Interaction present (n = 269)	***Interaction absent (n = 146)***	***OR*** (95% CI**)**	***P*-value**	***OR*** (95% CI)**	***P*-value**
Patient age (year)						
< 46	238	129	0.98 (0.52-1.85)	0.97	0.83 (0.42-1.62)	0.583
≥ 46	31	17				
Gender						
Female	133	59	1.5 (1.003-2.26)	0.04	1.48 (0.96-2.28)	0.072
Male	136	87				
Hospital stay (day)						
< 7	156	115	2.68 (1.68-4.27)	<0.001	2.02 (1.24-3.28)	0.005
≥ 7	113	31				
Number of drugs						
< 7	142	119	3.94(2.43-6.38)	<0.001	3.37 (2.05-5.54)	<0.001
≥ 7	127	27				

** Hosmer–Lemeshow goodness-of-fit test: p = 0.77*
***OR = Odds ratio; CI = Confidence interval*

Many drug interactions compendia have assigned different levels or grades to drug interactions based on their severity, onset, evidences in scientific literature [17,19,20]. Importance of such grading can not be ignored in clinical practice. All pDDIs are not equally harmful, therefore, identification of levels for each pDDI is integral to assessing clinical importance and appropriate management. For this purpose, we categorized all identified pDDIs into different levels. Our findings regarding the levels of pDDIs are consistent with other studies [3-5,13]. In our study, the major and moderate severity as well as good and fair documentation, identified for majority of pDDIs are of special concern. These findings indicate that the identified pDDIs have high potential to deteriorate patients' clinical condition or to alter therapeutic response. Consequently, careful monitoring will be needed.

The list in Table 4 should help physicians and clinical pharmacists to manage and prevent DDIs in psychiatric wards. The top 10 pDDIs are of special concern for practitioners as these interactions were of most common in our study. Divalproex sodium may increase the plasma levels of lorazepam and diazepam and can lead to toxicity including excessive sedation and respiratory depression. The patient should be monitored for evidence of such toxicity and dose should be adjusted accordingly. Concurrent use of haloperidol with promethazine or fluphenazine may result in an increased risk of cardiotoxicity including QT prolongation, *torsade de pointes* and cardiac arrest. Such combinations are better avoided, and if used, then close monitoring is required especially when starting, stopping or changing the dose of any interacting drug. Procyclidine may result in decreased serum-concentrations and effectiveness of phenothiazines (promethazine and fluphenazine) and enhanced anticholinergic effects including ileus, hyperpyrexia, sedation and dry mouth. Procyclidine and other anticholinergics (benztropine, orphenadrine and trihexyphenidyl) should not be used routinely with phenothiazine derivatives as prophylaxis against possible extrapyramidal symptoms. Their use should be reserved for those cases where reduction of the antipsychotic dosage is not possible. Anticholinergic use should be re-evaluated at least every three months.

Combination of haloperidol with olanzapine may lead to increased risk of Parkinsonism and the adverse effect may include cogwheeling rigidity and unstable gait.

Patients should be closely monitored for such adverse effects especially when olanzapine is added to haloperidol therapy. Haloperidol dosage may need to be decreased. Use of haloperidol with procyclidine or trihexyphenidyl may result in excessive anticholinergic effects including sedation, constipation and dry mouth. This combination should only be used when clearly indicated. Therapy should be closely monitored for excessive anticholineorgic effects and dosage may need to be adjusted. Combination of divalproex sodium with olanzapine may result in decreased olanzapine plasma concentrations. Therefore, plasma concentration of olanzapine should be monitored to ensure optimum response. Moreover, combination of divalproex sodium with olanzapine appears to increase the risk of hepatic injury. The authors of this report recommend monitoring of hepatic enzymes every 3 to 4 months for the first year of concurrent therapy, and then every 6 months if no adverse effects are detected [1,17,19,20].

Our findings regarding strong association of pDDIs with long hospital stay and taking increased number of drugs; and insignificant association with gender are consistent with other studies [5,6,8,9]. According to our findings, there was no significant relationship between old age and pDDIs that is inconsistent with other studies [5,7-10]. The possible reason for this inconsistency might be the small proportion of old age patients in our study population, i.e., 41(10 %) patients were of age 46 - 60 years and only 7(2 %) patients were older than 60 years (Table 1).

Limitations of the study

Potential limitations of this study include the following. The actual effects of the identified pDDIs were not evaluated. Studies are needed to identify actual clinical consequences of these interactions. The study population included a very small proportion of aged patients and the results might not have explored the pattern of pDDIs in these patients. Similar or higher prevalence rate of pDDIs in elderly psychiatric patients might be anticipated as evident from the survey of Vasudev and Harrison [14]. This study was carried out in a single institution and so its external validity is not known exactly and multicenter studies are therefore recommended. Micromedex Drug-Reax® System [17] was used for screening of pDDIs in this study while other screening resources were used by other researchers [12,14].

CONCLUSION

A high prevalence of pDDIs was recorded in the psychiatric ward studied, a majority of which were of moderate severity. Patients with long hospital stay and increased number of drugs were more exposed to pDDIs. Careful monitoring will be needed to manage and prevent negative clinical consequences of these interactions. Studies should be conducted to identify actual effects of these interactions.

ACKNOWLEDGEMENT

The authors are grateful to University of Peshawar for financial support. Thanks are due to the Consultant and other Staff of the Psychiatric Ward of ATH as well as to Mr. Jibran Hasan Khan of Ayub Medical College, Abbottabad; and Syed Muhammad Ashhad Haleemi, Department of Pharmacy, University of Peshawar for their cooperation during the study.

REFERENCES

1. *Baxter K (editor). Stockley's Drug Interactions. 9th Edition. London, Chicago: Pharmaceutical Press, 2010.*
2. *Zwart-van Rijkom JEF, Uijtendaal EV, Ten Berg MJ, Van Solinge WW, Egberts ACG. Frequency and nature of drug–drug interactions in a Dutch university hospital. Br J Clin Pharmacol 2009; 68: 187-193.*
3. *Cruciol-Souza J, Thomson J. A pharmacoepidemiologic study of drug interactions in a Brazilian teaching hospital. Clinics 2006; 61: 515-520.*

4. Fokter N, Mozina M, Brvar M. Potential drug-drug interactions and admissions due to drug-drug interactions in patients treated in medical departments. Wien Klin Wochenschr 2010; 122: 81-88.
5. Riechelmann RP, Moreira F, Smaletz Ò, Saad ED. Potential for drug interactions in hospitalized cancer patients. Cancer Chemother Pharmacol 2005; 56: 286-290.
6. Johnell K, Klarin I. 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 2007; 30: 911-918.
7. Nobili A, Pasina L, Tettamanti M, Lucca U, Riva E, Marzona I, Monesi L, Cucchiani R, Bortolotti A, Fortino I, et al. Potentially severe drug interactions in elderly outpatients: results of an observational study of an administrative prescription database. J Clin Pharm Ther 2009; 34: 377-386.
8. Gagne JJ, Maio V, Rabinowitz C. Prevalence and predictors of potential drug-drug interactions in Regione Emilia-Romagna, Italy. J Clin Pharm Ther 2008; 33: 141-151.
9. Doubova SV, Reyes-Morales H, Torres-Arreola LdP, Suarez-Ortega M. 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 2007; 7: 147.
10. Katona CLE. Psychotropics and drug interactions in the elderly patient. Int J Geriatr Psychiatry 2001; 16: S86-S90.
11. Moura CS, Acurcio FA, Belo NO. Drug-drug interactions associated with length of stay and cost of hospitalization. J Pharm Pharm Sci 2009; 12: 266-272.
12. Vonbach P, Dubied A, Krähenbühl S, Beer JH. Prevalence of drug-drug interactions at hospital entry and during hospital stay of patients in internal medicine. Eur J Intern Med 2008; 19: 413-420.
13. Egger SS, Drewe J, Schlienger RG. Potential drug-drug interactions in the medication of medical patients at hospital discharge. Eur J Clin Pharmacol 2003; 58: 773-778.
14. Vasudev A, Harrison R. Prescribing safely in elderly psychiatric wards: survey of possible drug interactions. Psychiatric Bulletin 2008; 32: 417-418.
15. Davies SJC, Eayrs S, Pratt P, Lennard MS. Potential for drug interactions involving cytochromes P450 2D6 and 3A4 on general adult psychiatric and functional elderly psychiatric wards. Br J Clin Pharmacol 2004; 57: 464-472.
16. Davies SJC, Lennard MS, Ghahramani P, Pratt P, Robertson A, Potokar J. PRN prescribing in psychiatric inpatients - potential for pharmacokinetic drug interactions. J Psychopharmacol 2007; 21: 153-160.
17. Anonymous. MICROMEDEX DRUG-REAX® System [database on CD-ROM].Volume 148. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. 2011.
18. Janchawee B, Wongpoowarak W, Owatranporn T, Chongsuvivatwong V. Pharmacoepidemiologic study of potential drug interactions in outpatients of a university hospital in Thailand. J Clin Pharm Ther 2005; 30: 13-20.
19. Tatro D (editor). Drug Interaction Facts: Facts and Comparisons. Wolters Kluwer Health, St. Louis, Missouri, 2009.
20. Hansten PD, Horn JR (editors). Drug Interactions Analysis and Management: Wolters Kluwer Health, Inc. St. Louis, MO, 2008.