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Original Article

Pharmacology Section

Evaluation of Potential Drug-Drug Interactions with Antidepressants in Two Tertiary Care Hospitals

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ABSTRACT

Background: Limited resources of healthcare system and high use of antidepressants have raised some serious concerns regarding proper surveillance system of prescribed medicines. Not much literature is available from Pakistan regarding the potential drug-drug interactions (pDDIs) associated with antidepressants.

Objective: The objective of this study was to assess the frequency of pDDIs associated with antidepressants, their severity, significance and their association with patient characteristics.

Materials and Methods: A prospective, observational study was conducted in two major hospitals of Karachi for the period of three months. Patient profiles, medication charts, and physician notes were thoroughly reviewed to gather all the relevant information. Inclusion and exclusion criteria were set prior to data collection. The collected data was then analysed using Micromedex Drug-REAX System. Descriptive and binomial logistic regression analysis was used to express results.

Results: Of 245 prescriptions reviewed, 141 prescriptions had at least one pDDI (57.5%). A total of 181 pDDIs were identified in prescription containing antidepressant. The ratio of pDDI per prescriptions was 0.78. 42.5% interactions were moderate in severity, 30% of interactions were rapid in onset, and 43% were considered as significant interactions. Polypharmacy (OR=3.41, p<0.001) and presence of chronic problems (OR=2.14, p=0.002) were significantly associated with the occurrence of pDDIs. Citalopram and diclofenac (11.6%) was commonly prescribed interacting pair in this study.

Conclusion: The findings of this study recorded high frequency of antidepressants associated pDDIs. Our results confirm the significant association of polypharmacy with the occurrence of pDDIs with antidepressants. Future studies are warranted to establish these results by including hospitals in different parts of the country.

Keywords: Pakistan, Poly pharmacy, Surveillance system

INTRODUCTION

A drug-drug interaction (DDI) can be defined as a phenomenon whereby presence of second drug alters the pharmacokinetic and pharmacodynamics profile of a first drug. While an antidepressant DDI is a subset of all DDIs in which one of the two administered drugs is antidepressant [1]. However, potential drug-drug interaction (pDDI) does not occur in every patient and/or with the same intensity, as it depends on patient related factors and information about the effects of the interaction [2]. pDDI is an important component of adverse event (AE). The Food and Drug Administration (FDA) has defined AE as an unfavourable and unintended sign, symptom, or disease associated with the use of medicinal product. The association of pDDI and antidepressant is of great clinical relevance. The duration of use of antidepressants is from many months to years, during which many other drugs can be added or stopped. Researchers have reported that 30-35% patients in primary healthcare and outpatient clinics take, on an average, three drugs in addition to antidepressants. These findings are of great concern from public health perspective as it puts them at great risk of pDDIs [3].

The practice of polypharmacy is a huge concern for pDDIs. Drug therapy becomes more complex with polypharmacy. It leads to increase morbidity, mortality and increase healthcare expenses [4]. The pharmacists are greatly positioned in the healthcare system, which gives them the opportunity to suggest pharmacotherapy that is not only effective but also safe. The monitoring of pDDIs is not only required for drugs which are relatively contradicted, it is equally important for combinations which are considered beneficial in certain conditions. Several studies have been conducted to assess the frequency of pDDIs worldwide [5-7]. Majority of the studies have shown greater number of pDDIs associated with antidepressants. In Pakistan, not many researchers have explored this area. However, a study conducted in Peshawar, showed that 64.8% prescriptions has at least 1 pDDI in the psychiatric ward [8].This highlights the importance of early recognition of pDDIs in healthcare settings in order to maximize the effectiveness of drug combination while avoiding toxicity.

According to World Health Organization (WHO), healthcare system in Pakistan lacks a proper surveillance system. This is mainly because of the scarcity of health system and policy research. In hospital settings, doctors and other healthcare professionals are overburdened [9]. Importantly, average number of medications prescribed in Pakistan is relatively in higher than other parts of the world. Limited data is available from Pakistan on the subject of pDDIs, and very few studies have investigated this issue with the use antidepressants. Researchers have emphasized on the need to assess the pattern of pDDIs associated with antidepressants in Pakistan [8,10]. On the basis of above mentioned facts, it can be anticipated that the risk of medication errors including pDDIs is relatively high in healthcare settings of Pakistan. In view of this, we conducted this study to identify the frequency of pDDIs associated with the use of antidepressants, their levels, and association with patient characteristics.

MATERIALS AND METHODS

The study was conducted in two major tertiary care, teaching hospitals of Karachi, the biggest metropolitan city of Pakistan. Profiles of the patients were reviewed from different wards of the hospital including psychiatric ward, internal medicine, gastroenterology,

urology, surgical, cardiology, pulmonology high dependency unit and intensive care units. Both the hospitals are the major referral tertiary care hospital caters the population of approximately 25 million. Each hospital comprised of at least 300 beds, had all the major healthcare facilities in the hospital including laboratory and healthcare services. A prospective, observational study was carried out for the period of three months in the studied hospitals. All those profiles in which antidepressants were prescribed were included in this study. Patient profiles, medication charts, and physician notes were thoroughly reviewed to gather all the relevant information. Prescriptions of antidepressants were also identified from the pharmacy department. Data was collected by one of the authors responsible for data collection.

A sample size of antidepressant prescriptions were generated by using previously established formula for sample size calculation [11]. A sample size of 245 was calculated by keeping the anticipated prevalence of 20% [12], 5% margin of error (d=0.05), and 95% confidence interval (z=1.96) in a following formula–

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

where,

n = sample size

z = z-statistic for a level of confidence

p = anticipated prevalence or proportion

d = margin of error

Profiles of the patients aged 18 years and above, both male and female, admitted in any ward of the hospital, and prescribed with antidepressants for at least one day, were included in this study. Prescriptions were excluded from this study in case of ambiguity in interpretation of the data. Local products like creams, ointments and drops were also excluded from the analysis. The data was collected on the pre-design data collection form designed by the authors. The questionnaire included all the relevant information like demographic information, prescriber notes, medication chart, medical notes, past and current medical problems, to achieve the objectives of the study.

The data were then analysed for pDDIs by using drug interaction software, Micromedex Drug-REAX System (Thomson Reuters Healthcare Inc., Greenwood Village, Colorado, United States) [10]. This software has been widely used to analyse pDDIs in previously published literature [10,13,14]. The software displays all the relevant information about the interactions, including its mechanism and possible outcomes of the interaction. The interactions were then classified on the basis of onset, severity and documentation. Descriptive and binomial logistic regression analysis was used to express the results in frequency and percentages, and to explore the association between dependent and independent variables respectively.

Onset

Rapid: Within 24 hours

Delayed: Days to weeks

Severity

Contraindicated: Combination is contraindicated

Major: Life threatening or permanent damage

Moderate: Deterioration of patient's status

Minor: Bothersome or little effect

Documentation: It is a confidence that an interaction can occur. This evaluation is based on supporting biomedical literature.

Established: Occurrence of interaction is supported by well controlled studies

Probable: Very likely, but not proven clinically

Suspected: May occur, data is available but needs more study

Possible: could occur, but data is limited

Unlikely: Doubtful, no evidence available.

Level of Significance: It relates to the magnitude of the effect, to the likelihood of occurrence, and subsequently, to the necessity of monitoring the patient or altering therapy to avoid potentially adverse consequences. It is classified as significant or non-significant.

RESULTS

A total of 245 prescriptions of antidepressants were reviewed for the period of 3 months in studied hospitals, in which 141 prescriptions had at least one pDDI (57.5%). A total of 181 pDDIs were identified which gives the rate of 0.78 interaction per prescription. Majority of the patients were male (66.9%) as compared to their female counterpart. A large of proportion of patients fell in the age range of 40-49 years followed by patients aged 50 years and above (26.1%). More than half of the patients had been prescribed more than six medications. Approximately two thirds of the patients were admitted with chronic medical problems (68.6%). The complete information about the demographic variables is presented in [Table/Fig-1].

The results showed that majority of the pDDIs were of moderate severity (42.5%), while major interactions and absolute contraindications contributed about 17.1% and 10% of the total interactions respectively. Approximately 30% of interactions had rapid onset of action as compared to 70% of delayed onset pDDIs. Majority of the pDDIs were suspected in relation to the scientific evidences (44.2%), while established pDDIs accounted for 17.7% of the total DDIs. The proportion of probable and possible interactions was 17.1% and 21% respectively. Frequency of pDDIs based on severity and onset and documentation is summarized in [Table/Fig-2].

The findings of this study revealed no significant differences between the frequency of pDDIs in male and females, although pDDIs were slightly lower among females (OR=0.77, p=0.541). The results were not different when the analysis showed no significant difference in the frequency of pDDIs between younger (18-29 years) and older (≥50 years) patients (OR=1.24, p=0.177). In contrast, patients who had more than six medications in their prescriptions were more likely to had a case of pDDI than those prescribed with <3 medications (OR=3.41, p<0.001). The appearance of pDDIs were also more likely in patients with chronic medical problems than contrasting group (OR=2.14, p=0.002).Binary logistic regression analysis is tabularized in [Table/Fig-3]. 43% of the total DDIs were significant as shown in [Table/Fig-4].The combination of citalopram and diclofenac (11.6%), imipramine and labetalol (10.5%), and fluoxetine and propranolol (9.39%) were more prevalent in this study than others [Table/Fig-5].

Variables	n	%
Gender		
Male	164	66.9
Female	81	33.1
Age (years)		
18-29	38	15.5
30-39	56	22.8
40-49	87	35.6
≥50	64	26.1
Medication per patient		
<3	49	20
3-6	69	28.1
>6	127	51.9
Patient with chronic medical problems		
Yes	168	68.6
No	77	31.4

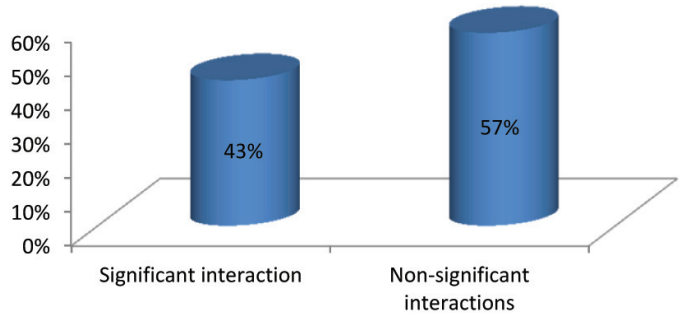
[Table/Fig-1]: Demographic information of the participants
Note: Total numbers of patients were 245

Levels	n	%
Severity		
Contraindicated	18	10
Major	31	17.1
Moderate	77	42.5
Minor	55	30.4
Onset		
Rapid	54	29.8
Delayed	127	70.2
Documentation		
Established	32	17.7
Probable	31	17.1
Suspected	80	44.2
Possible	38	21

[Table/Fig-2]: Frequency of pDDIs based on severity and onset and documentation.
Note: Total numbers of DDIs identified were 181

Variables	Interaction (%)		Multivariate OR^ (95% CI)*	p-value
	Yes	No		
Gender				
Male	67.4	32.6	Ref	
Female	61.7	38.3	0.77 (0.23-1.1)	0.541
Age				
18-29	51.3	48.7	Ref	
30-39	58.2	41.8	1.13 (0.54-1.54)	0.763
40-49	60.1	39.9	1.47 (0.63-1.89)	0.130
≥50	58.7	41.3	1.24 (0.45-1.77)	0.177
Medication per patient				
<3	51.6	48.4	Ref	
3-6	60.7	39.3	1.65 (0.67-2.97)	0.087
>6	76.8	23.2	3.41 (1.1-5.56)	<0.001
Patient with chronic medical problems				
No	48.1	51.9 32.8	Ref	
Yes	67.2		2.14 (0.58-3.98)	0.002

[Table/Fig-3]: Binary logistic regression analysis.
^ Odds ratio
* Confidence interval
Note: Overall predictive accuracy is 74.7%.
Omnibus tests of model coefficients: Chi square value=19.872, p<0.05.
-2 Log likelihood=289.893, Nagelkerke R square=0.098
Hosmer and Lameshow test: Chi square value=12.168, p>0.05



[Table/Fig-4]: Level of significance of pDDIs

DISCUSSION

This study explored the frequency, severity, onset, documentation, and significance of DDIs associated in antidepressants. The study also highlighted the interacting drugs frequently prescribed concurrently with antidepressants, and also the association of DDIs with patient characteristics. To the best of our knowledge, this is the first study which specifically explored the pDDIs associated with antidepressants in the metropolitan city of Karachi. The occurrence of pDDIs in prescriptions with antidepressants (57.5%) was relatively higher than other studies conducted around the world [15,16]. In contrast, the occurrence of pDDIs reported in current research is slightly lower than another study conducted in psychiatric ward of tertiary care hospital [8]. We speculate that the lack of proper surveillance system, and the limitation of the use of information for medical decision are major reasons of increase in pDDIs in Pakistan. This speculation is also supported by World Health Organization [17]. However, the results suggest that number of pDDIs per patient was 0.78, which is lower than 1.3 (in psychiatric ward) reported by other researchers [18].

Interactions	n	%
Sertraline + Zolpidem	6	3.31
Citalopram + Metoclopramide*	5	2.76
Citalopram + Trazodone*	1	0.55
Fluoxetine + Zolpidem	2	1.1
Citalopram + Morphine	3	1.66
Fluoxetine + Carbamazepine	4	2.21
Venlafaxine + Tramadol	4	2.21
Fluoxetine + Metoclopramide*	13	7.18
Citalopram + Tramadol*	9	4.97
Amitriptyline + Fluconazole	5	2.76
Imipramine + Labetalol	19	10.5
Amitriptyline + Carbamazepine	6	3.31
Amitryptyline + Thyroxin	3	1.66
Escitalopram + Tramadol*	14	7.73
Imipramine + Escitalopram*	6	3.31
Sertaline + lithium	5	2.76
Ibuprofen + sertraline	4	2.21
Amitriptyline + Omeprazole	8	4.42
Diclofenac + Fluoxetine*	12	6.63
Fluoxetine + Propranolol*	17	9.39
Citalopram + Ibuprofen	14	7.73
Citalopram + Dicolfenac	21	11.6

[Table/Fig-5]: Common interacting drug combinations
Note: Total numbers of DDIs identified were 181
* Significant DDIs

Most of the DDIs were moderately severe in present study, which is in line with other published studies [19,20]. However, we could also not ignore the occurrence of major interactions (17.1%) as it may lead to fatal consequences if not managed promptly. This is mainly because of the lack of standardization in healthcare system of Pakistan. The deficiency of health services and irrational practice of medicines are crucial problems [21]. It is therefore important to establish clinical pharmacy services to optimise the use medicines in Pakistan. A significant proportion of the pDDIs had a rapid onset of actions in this study. This figure is highly alarming as it could cause rapid deterioration of patient health. It urges on the need to closely monitor the patients prescribed with antidepressants as patients are at high risk to destructive outcomes of pDDIs.

It is noteworthy to discuss the association of patient characteristics with the frequency of pDDIs. Number of medications was directly proportional to the frequency of pDDIs as it was noted that the likelihood of pDDIs was higher when more than 6 medicines were prescribed in a prescription containing one or more antidepressants. These results are in accordance to other related studies [8,22]. Special caution is warranted, in view of these findings, when prescribing medicines concurrently with antidepressants. Researchers have previously reported the practice of polypharmacy by the physicians in Pakistan [23,24]. These findings are also supported by another result of this study which showed the likelihood of pDDIs in case of chronic problems. We assume that the presence of chronic diseases have led the prescribers to prescribe multiple drugs. However, it is pertinent to take necessary measures to ensure the appropriate use antidepressants by effective utilization of antidepressants based on scientific evidences. We believe that continuous medical education could serve as an effective tool, where we can introduce such topics

to optimise prescribing practices among physicians. Researchers believe that the age is also a significant predictor of pDDIs as elderly people are more at risk of CYP3A4 interactions [22]. Our results also support this hypothesis as the frequency of pDDIs was relatively higher in older patients, though the results were not supported by statistical significance. We suggest that consideration should be given to include common cytochrome P450–related drug interactions in the prescribing chart.

Various studies have reported common interacting pairs associated with antidepressants. Citalopram and procyclidine [8], Flouxetine and Temazepam [22] were among the major interacting pairs reported by other researchers. However, in this study, combination of citalopram and diclofenac was frequently prescribed in studied hospitals. The reason of this discrepancy could be explained by the fact that the referenced studies were mainly confined to psychiatric ward, while our main focussed was on prescription with antidepressants irrespective of the wards. Additionally, metoclopramide was another drug which appeared to be interacting with antidepressant drugs mainly citalopram and fluoxetine. It has been reported that the use of metoclopramide with these antidepressants is moderately associated with the development of selective serotonin reuptake inhibitors and extrapyramidal symptoms. It has been proposed that competitive inhibition of CYP450 2D6 isozyme is the major mechanism of this interaction [5]. We propose that these combinations should be closely monitored to ensure its optimum response.

The strength of this study is that it has explored an area where not much literature is available. This study would add significant value to the existing literature. This study would also encourage the researchers to explore this area by covering other major referral hospitals of the country.

LIMITATIONS

The study also has some limitations like any other study. Results should be interpreted with great caution as inclusion of two hospitals may not justify the generalizability to the whole population, and the possible interaction between the variable variables in the statistical analysis may have affected the findings of this result. Another limitation of this study is its limited time duration without any intervention component.

CONCLUSION

This study showed relatively high frequency of pDDIs associated with antidepressants. The findings also confirm the association of polypharmacy with pDDIs. Attention should be diverted to prevent and manage such interactions to promote well-being of the patients. Establishment of clinical pharmacy services in the hospital setting could play a vital role in addressing this issue. However, more studies are warranted to further establish these results in different hospitals of Pakistan.

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