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PATTERN & PREDICTORS OF DRUG-DRUG INTERACTIONS AMONG THE PATIENTS ADMITTED IN NEUROLOGY AT A TERTIARY CARE HOSPITAL - A CROSS-SECTIONAL STUDY

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ABSTRACT: Objective: Drug - drug interactions (DDI) is a permanent risk in patients with complex therapeutic regimens. Drugs commonly prescribed in Neurology contribute for most of the potentially hazardous DDI. The present study was undertaken to identify the DDI and its predictors among the patients admitted in Neurology ward. **Material and Methods:** An analytical cross-sectional study was conducted from January – May, 2015 among the patients admitted in Neurology wards. All the patients on at least two drugs were enrolled. Drug data was analyzed for interactions using the standard drug interaction software. **Results:** Among 110 enrolled patients, 289 hazardous DDIs were identified, of which 261 were potential DDIs (pDDIs). Atorvastatin and Pantoprazole (14%), Aspirin and Low Molecular Weight Heparin (13%), and Atorvastatin and Clopidogrel (13%) were the most commonly interacting pairs. Commonly encountered antiepileptic pairs that led to pDDIs were Phenytoin and lorazepam (7%) and clobazam and levetiracetam (7%). Majority of interactions were of moderate (72%), followed by major (20%) severity. 69% of DDIs required therapeutic monitoring and 19% required therapeutic modification. Number of prescribed drugs, length of hospital stay, co-morbid conditions and number of anti-epileptic drugs prescribed were identified as the predictors for the development of DDIs [$p < 0.05$]. **Conclusions:** 46.3% of the patients admitted in Neurology wards were prescribed with drugs that could lead to DDIs. Majority of the DDIs were moderate in severity and required therapeutic monitoring. Hence, intense monitoring programme needs to be initiated in every hospital for early detection and prevention of DDIs.

INTRODUCTION: Therapeutic regimens have become complex due to increasing burden of diseases and newly introduced drugs that are claimed to be safer and more efficacious [1]. These complex therapeutic regimens often expose the patients to potential drug - drug interactions (DDIs). DDIs occur when the effects of one drug are changed by the presence of another drug(s), food, and drink leading to an unexpected change in the condition of the patient [2].

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Clinically significant drug interactions, which pose potential harm to the patients, may result from changes in pharmaceutical, pharmacokinetic, or pharmacodynamic properties. Pharmacokinetic interaction occurs when either of the concurrently administered drugs have potential to alter other's pattern of absorption, distribution, metabolism and excretion. Similarly, pharmacodynamic interaction occurs if concurrently administered drugs have similar or opposite effects [3].

Various studies have shown that potential DDIs cause adverse effects and changes in therapeutic efficacies of the combined medicines, with consequent poor control of the diseases under treatment [4, 5]. It is estimated that DDIs account for approximately 2.8% of hospital admission every

years [6]. Intense monitoring of DDIs has been shown to minimise the risk of ADEs in hospitalized patients.

The burden of Neurological disorders in India is estimated over 30 million which often warrant complex therapeutic regimen [7]. Treatment in neurology ward are challenging due to the existence of co-morbidities that demands polypharmacy. Recent study in Iran has reported that in 35.5% of the patients in neurology ward encountered with at least one pDDIs [8].

A thorough literature search did not reveal any published report on DDIs in neurological disorders in Indian population. The present study was initiated to determine the incidence of DDIs in patients admitted to neurology wards and to identify risk factors for the development of pDDIs

MATERIALS AND METHODS:

Setting and Study Design:

The analytical cross-sectional study was undertaken for the period of 6 months from Dec – 2014 to May 2015 at the Department of Neurology of Victoria Hospital, attached to Bangalore Medical College & Research Institute, a tertiary care teaching hospital in Southern India.

Study Population:

Patients with neurological disorders, aged 18 years or older admitted to the Neurology ward with a hospital stay of at least 24 h, those prescribed two or more drugs and consenting for the study were enrolled.

Data collection:

The case records of 110 consecutive patients who had been admitted to the Neurology ward between December 2014 and May 2015 were independently reviewed for relevant data by two physicians. All relevant data (physician and nursing notes, investigations performed and medication order records) were included in the study. Relevant data on demographics (age, gender, and religion), clinical characteristics (complete diagnosis, co-morbid conditions and length of stay in the hospital) and treatment (drugs prescribed, duration of therapy, and no. of drugs) were collected in a specially designed case record form.

Definitions:

Based on definitions used in the literature, we defined DDI as "Pharmacologic or clinical response to the administration of a drug combination, different from that anticipated from the known effects of the two agents when given alone" [9].

DDI assessment and analysis:

Each DDI was assessed independently by two investigators, using drug interactions software for mechanism, level of evidence, and severity and the level of agreement determined. Whenever there was disagreement among the two reviewers, consensus was reached following discussion with a review panel. The review panel consisted of a medical doctor who is also a Pharmacovigilance expert and a senior research officer with sufficient expertisation in the analysis of DDIs. Disagreements were sorted out and included in the final analysis. Each drug was considered only once for the same patient for the analysis.

Renal dysfunction was defined based on the estimated creatinine clearance (ml/min) values calculated using the Cockroft–Gault equation. Values of 120 ml/min/1.73 m^2 for men and 100 ml/min/1.73 m^2 for women were considered normal.

The data of patients were further subdivided into two groups based on the occurrence of DDIs: those patients who developed one or more DDIs after admission in the Neurology wards and those who did not develop DDIs during their stay in the Neurology ward. These two groups of patients were compared for the various characteristics of DDIs.

Tools Used:

Pre-designed proforma was used to record the prescribed medications, doses, dosing intervals and length of drug use. The drugs prescribed to the patients during hospital stay were analyzed for possible drug-drug interaction by drug interaction software Lexicomp, version 1.91 [10]. DDIs were classified into established (The existence of the drug interaction has been clearly established by the controlled studies), probable (The existence of drug interaction is suggested by documentation, but well controlled studies are lacking), possible (Available

documentation is poor), suspected (Documentation is scant; however, the possibility of a clinical conflict exists) and unlikely (Documentation as well as a sound pharmacological basis is lacking) based on the documentation status. Based on the severity DDIs were subdivided into Major (life-threatening or permanent damage), Moderate (deterioration of patient's status) and Minor (bothersome or little effect) categories [11].

Statistical Analysis:

The data collected were subjected to descriptive analysis to study the characteristics of the DDIs. Results were expressed as percentages, as mean ± standard deviation (SD) for continuous parametric variables. Comparisons between the DDI and non-DDI groups were performed using the chi-square and t tests as appropriate. P value < 0.05 was considered as statistically significant.

Multivariate logistic regression analysis was done to control multiple predictors for developing DDIs. The explanatory variables considered for the first step of the regression analysis include relevant data on demographics (age, gender), co-morbid conditions (congestive cardiac failure, renal dysfunction, lower respiratory tract infections, hypertension, and diabetes mellitus), length of hospital stay and number of drugs as well as antiepileptic drugs (AEDs) prescribed. Variables that were associated with a significance level of <0.2 on the univariate analysis were subjected to multivariate binary logistic regression analysis. Statistical analysis was performed using statistical software R version 3.2.0.

Ethics: The study was conducted following the approval from the Institutional ethics committee of Hospital. Socio demographic data was obtained from the patients in pre-structured case record form after getting their written informed consent. Study was carried out in compliance with the Declaration of Helsinki (DOH) and Indian Good Clinical Practice (GCP) guideline.

RESULTS:

Demographic characteristics: Prescriptions of 110 consecutive patients admitted to Neurology in-patient department were reviewed. Among these 51 (46.3%) were identified with at least one DDIs. A total 289 DDIs were identified. 44 (40%) patients were identified to develop two DDIs, 21(19.1%) patients were identified to develop five or more DDIs, and 8 (7.3%) patients were identified to develop ≥ 10 DDIs. Among these 110 patients, 65 (59.09%) were males. Approximately 58 (52.7%) patients belonged to Hindu community, 35 (31.82%) patients belong to Muslim community and 17 (15.45%) patients were Christians.

The mean age of the patients in the DDI and non-DDI groups was (39.72±15.28 vs 39.32±10.1 years, respectively; p=0.19). Patients in the DDI group had a significantly longer duration of stay in the hospital, more co-morbidities (1.74±1.62 vs 1.05±1.31, p <0.001), received more medications and AEDs than patients in the non-DDI group (**Table 1**).

TABLE 1: **COMPARISON OF CHARACTERISTICS BETWEEN THE DDI AND NON-DDI GROUPS OF PATIENTS IN NEUROLOGY WARD**

Characteristics	Non DDI group (n = 59)	DDI – group (n = 51)	p value
Age, mean ± SD	39.32±10.1	39.72±15.28	0.19≠
Gender			
Male (%)	32 (29)	33 (30)	0.36*
Female (%)	27 (25)	18 (16)	
Number of co-morbidities, mean ± SD	1.05±1.31	1.74±1.62	0.0001≠
Duration of hospital stay (days) mean ± SD	8.74±4.9	10.88±5.85	<0.001≠
Frequency of prescription with >5 drugs (%)	22 (20)	41 (42)	<0.01*
Frequency of antiepileptic prescription (%)	24 (22)	29 (26)	<0.01*

Data are given as the number (n) of patients with the percentage in parentheses, or as the mean ± standard deviation (SD)
*Chi-square test for significance (p<0.05)
≠ t-test for significance (p<0.05)

Among the 110 patients, the most common co-morbid conditions were Diabetes mellitus (DM) (50 patients, 45%), Hypertension (44 patients, 40%), Lower respiratory tract infection (LRTI) (27 patients, 25%), Congestive heart failure (CHF) (11 patients, 10%), Dyslipidemia (16 patients, 15%), Renal dysfunction (8 patients, 7.2%). Comparison of the rate of co-morbidities between patients with DDIs and those without DDIs are presented in **Table 2**

TABLE 2: COMPARISON OF CO-MORBIDITIES BETWEEN THE DDI AND NON-DDI GROUPS OF PATIENTS IN NEUROLOGY WARD

Co-morbid condition	Non DDI-group (n = 59)	DDI – group (n = 51)	p value*
Hypertension (%)	16 (15)	28 (25)	0.55
Diabetes mellitus (%)	19 (17)	31 (28)	0.6
Congestive heart failure (%)	5 (4.5)	6 (5.5)	1.01
Renal dysfunction (%)	4 (3.6)	4 (3.6)	1.00
Dyslipidemia (%)	5 (5)	11 (10)	0.37
Lower respiratory infection (%)	12 (11)	15 (14)	0.09

Data are given as the number (n) of patients with the percentage in parentheses

*Chi-square test for significance ($p<0.05$)

Inter-observer agreement:

Two reviewers independently assessed DDIs for mechanism, severity and level of documentation using the Lexicomp DDIs checker software. The Cohen's weighted kappa score for inter reviewer agreement was 0.751 for mechanism, 0.585 for level of evidence and 0.495 for severity. Thus, there was a moderate to substantial level of agreement between the reviewers for all parameters assessed.

Drug data analysis:

A total of 110 patients were prescribed with 768 numbers of drugs. Hence the average number of drugs prescribed per patient was 6.98 $\pm$ 3.59. Among the total of 768 medicines 81 were antiepileptic drugs. AEDs constituted 10% of total drugs prescribed. Antimicrobials (14%), antiepileptics (10%) and antihypertensive (5%) were prescribed most frequently. Different type of drugs prescribed to the patients admitted in neurology ward is shown in **Fig.1.**

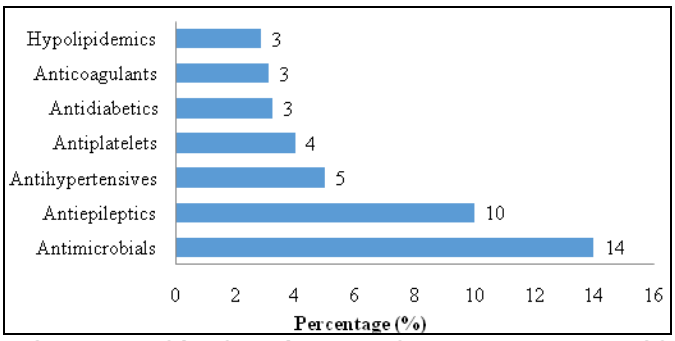

FIG. 1: UTILISATION PATTERN OF DIFFERENT DRUGS IN NEUROLOGY WARD

Drug – drug interactions:

A total of 289 DDIs were identified, among them 261 (90.31%) were pDDIs. Significant proportion of drug-drug interactions were of moderate severity 204 (72%) while 57 interacting combinations identified were of major severity (20%) and 22 (8%) are of minor severity. Among 289 DDIs identified, 22 (8%) had established status of documentation, 100 (35%) had probable documentation status, 157 (54%) were of suspected documentation status and 10 (8%) had possible documentation status (**Fig.2**).

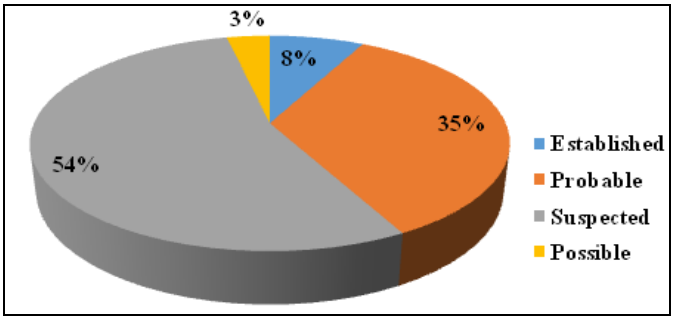

FIG.2: LEVEL OF DOCUMENTATION OF DDIS

DDIs encountered were analyzed on the basis of mechanism of interaction. In total, 128 (48%) DDIs was of pharmacokinetic type, 116 (40%) were of pharmacodynamic type and remaining 34 (12%) were of unknown mechanism. The most common interacting pairs identified in this study were Atorvastatin/ Pantoprazole (40 [14%]), aspirin/low molecular weight heparin-LMWH (38[13%]), Atorvastatin/ Clopidogrel (38 [13%]) and Ceftriaxone/Acenocoumarin (26 [9%]) (**Fig. 3**).

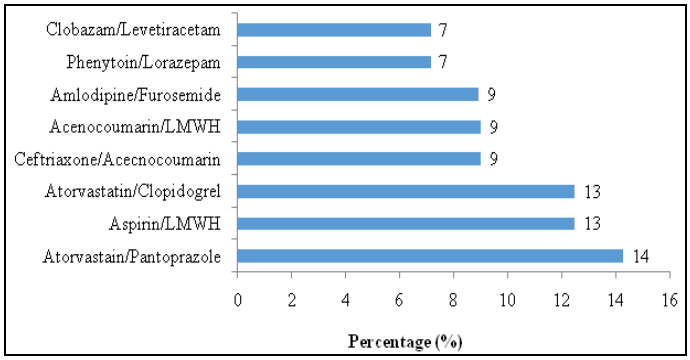

FIG.3: COMMONLY INVOLVED INTERACTING DRUG PAIR IN NEUROLOGY WARD

Possible outcome of the serious DDIs: Acenocoumarin & LMWH (26 [9%]) and Acenocoumarin & Aspirin [8(%)] are the frequently encountered interacting pair responsible for major severity of DDIs which can lead to serious adverse consequences. Important interacting pairs of major severity along with the possible hazardous outcomes and possible measure to avoid those interactions are enlisted in the **Table3**.

TABLE 3: DDIS OF MAJOR SEVERITY WITH POSSIBLE ADVERSE CONSEQUENCES

Drug interacting pairs	Possible Consequences	Suggestive action	Frequency of encounter [%]
Acenocoumarin &LMWH	Bleeding event	Therapeutic monitoring	26 [9]
Acenocoumarin &Aspirin	Bleeding event	Therapeutic monitoring	8 [3]
Atorvastatin & Carbamazepine	Reduced effect of Atorvastatin	Therapeutic modification	6 [2]
Aripiprazole & Levodopa + Carbidopa	Reduced effect of levodopa	Therapeutic modification	3 [1]
Aspirin & Ibuprofen	Decreased Cardio-protective effect of Aspirin	Therapeutic modification	3 [1]
Escitalopram & Ofloxacin	QT prolongation	Avoid combination	2 [0.6]
Carbamazepine & Amlodipine	Decreased effect of Amlodipine	Therapeutic modification	4 [3.6]

Predictors for occurrence of DDIs in Neurology in-patent department: The multivariate logistic regression analysis showed that patients with increased duration of hospital stay [Odds Ratio (OR)- 1.75, 95% Confidence Interval (CI)- 1.11-3.49, p value <0.05], prescribed with AEDs [OR-2.49, 95% CI-1.25-9.8, p value <0.05], and patients prescribed with higher no. of drugs [OR- 2.73, 95% CI- 1.3-9.42, p value <0.05], had a higher risk of experiencing DDIs in the Neurology in-patient department (**Table 4**).

TABLE 4: PREDICTORS FOR OCCURRENCE OF DDIS IN NEUROLOGY WARD

Variables	β-coefficients	p value	Odds ratio (OR)	95% confidence interval
Age	-0.0016	0.09	1.00	0.89-1.10
Duration of hospital stay	0.55	0.04	1.75	1.11-3.49
Prescription with AEDs	1.28	0.01	2.9	1.2-9.8
Number of medications	1.003	0.03	2.73	1.3-9.42
Number of co-morbidities	0.73	0.29	2.09	0.67-11.17

DISCUSSION: Clinically significant DDIs are important, but under reported source of medication errors. They may pose potential harm to the patients. Timely intervention by health care professionals can prevent DDIs and thereby reduce the occurrence of ADRs.

About 46.3% of the patients admitted in the Neurology wards were noted to have atleast one DDIs, of which 91% were pDDIs. Patel et al reported 30.67% of pDDIs in Cardiology wards at a South Indian teaching Hospital and Sharma et al noted 21.3% pDDIs in the cardiac unit of General

Medicine in Nepal [12, 13]. The incidence at Neurology wards in Iran was reported to be 35.5%[8]. The higher incidence rate of pDDIs noted in the present study could be due to increased average number of drugs per patient (6.98 ± 3.59), polypharmacy (42%) and increased prescriptions of AEDs (26%).

We noted a majority of Pharmacokinetic type of interaction (48%) compared to Pharmacodynamic type (40%). Sharma S et al noted 58% of pharmacokinetic and 22% of pharmacodynamic interactions among hospitalized cardiac patients [13].

72% of the pDDIs were of moderate severity and 20% were considered to be major in severity. The studies in Nepal and India showed similar results [12, 13, 14]. DDIs that are major in severity could be life threatening and hence prescription of such interacting pairs of drugs should be prevented.

The most common interacting pairs of drugs noted in the study were Atorvastatin/ Pantoprazole 14%, Aspirin/low molecular weight heparin 13% and Atorvastatin/ Clopidogrel 13%. Potential DDIs involving Atorvastatin was the highest 27% followed by LMWH 22%. This could be due to higher prescriptions of Atorvastatin (3%) and LMWH (3%) in Neurology wards. LMWH is associated with pDDIs with major severity (9%) as they could lead to life threatening bleeding.

We found that the number of prescribed medications, number of co-morbidities and length of hospitalization were the contributing risk factors for the occurrence of DDIs, as determined by the multiple logistic regression model. The risk of encountering DDIs in patients receiving more than 5 drugs was 2.73 times more than the patients receiving less than 5 drugs. A study conducted in Iran among patients admitted in neurology reported that incidence of DDIs increased by 6.91 times in patients receiving more than 5 drugs [8]. A study by Sharma S et al. from Nepal found a linear relationship between the number of drugs per prescription and the frequency of DDIs [13]. Kashyap M et al form India also found number of drugs as an independent predictor of DDIs [15]. Logistic regression analysis predicted AEDs as a potential risk factor [OR- 2.49, 95% CI-1.25-9.8, p <0.05] for the development of DDIs as reported by many previous studies [16, 17]. AEDs are involved especially in pharmacokinetic interactions. AEDs are potential enzyme inducers (Carbamazepine, Phenobarbital, Phenytoin, Primidone) or inhibitors (valproic acid), resulting in a decrease or increase in the serum concentration of AEDs. Conversely, serum concentrations of AEDs may be increased by other enzyme inhibitors and decreased by enzyme inducers.

The length of hospital stay was significantly different between the DDI and non-DDI group (10.88±5.85 vs 8.74±4.9, p <0.001). A significant relationship was found between the length of hospital stay and DDIs in regression analysis. Our finding well resembles the finding by previous studies [8, 13, 18]. As the length of hospital stay increases, the number of prescribed medication also increases and thereby increasing the risk of DDIs and ADRs.

The risk of DDIs did not increase with age (OR-1.00, 95% CI, 0.89-1.10, p=0.09). Namazi S et al reported that age and gender did not influence the development of DDIs in Neurology wards which also matches with the study conducted by Kappa PA et al in South Africa [8, 19]. But these findings are in contrary to most of the previous studies [20, 21]. Such discrepancy can be explained in terms of the population enrolled in our study where mean age is 39.72±15.28 years in DDI group. In a more heterogeneous study population with large sample, age factor could influence DDIs.

This study has certain limitations. Firstly, this study was conducted in the Neurology ward of a teaching hospital, and hence, the results obtained are difficult to generalise. Secondly, one software (Lexicomp drug interaction software) was used in the present study. Thirdly, our patients were only monitored during hospitalization period. So, ADRs and DDIs occurring after hospital discharge could not be detected. Finally larger sample size and longer study period could have been helpful to identify the other predictors of DDIs. Hence, accurate assessment of pDDIs outcome, thorough patient's specific evaluation with a proper hierarchical system to monitor DDIs could reduce the burden of DDIs in hospitals.

CONCLUSION: Potentially hazardous DDIs are common among the patients admitted in Neurology ward. Increased number of prescribed drugs, prolonged hospital stay, co-morbid conditions and number of anti-epileptic drugs were the risk factors significantly associated with DDIs.

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