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Drug -Drug Interactions In Neurosurgical Treatment

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ABSTRACT

The present study was a cross-sectional retrospective study, carried out by using automated medication records of 280 randomly selected patients who had been admitted to neurology ward and receiving at least two medications. Initially, demographic information of patients such as age, gender, and clinical diagnosis were recorded and incomplete patients' records were excluded from the study. The entries of all prescribed drugs to the selected patients from the date of admission till the date of discharge were made. Patients with major severity were screened out. Categorization of clinically potential DDIs was made on basis of Onset, severity and scientific evidence. Among 280 patients of neurosurgical ward 201 patients had the drug-drug interactions and remaining 79 patients were not found any drug-drug interactions. In total of 638 drug-drug interactions some documented and which are categorized as excellent 84, good 180, fair 310 and some are not documented 64 drug interactions. Based on the severity of drug-drug interactions the potential drug-drug interactions categorized as contraindicated in 26 (04.32%) patients, major severity in 399 (62.50%) patients, moderate severe in 199(31.01%) and minor severity in 14(02.01%) patients.

Keywords: Neuro surgery, pDDIs, drug - drug interactions, Micromedex.

1. INTRODUCTION

Drug interactions are a leading cause of preventable adverse reactions any drug-drug (or food, supplement or herbal product) combination has the potential for producing an interaction. With 2.8 billion outpatient prescriptions filled in 2000, (10 per person in the United States) there are frequent opportunities for drug interactions to occur. Both the medical literature and extensive compendia enumerate a staggering number of interactions. In reality, some drug interactions are critical for optimum patient care such as combined use of drugs for their additive or synergistic effects, whereas others, although academically interesting, have little clinical relevance. The clinician, therefore, must be able to distinguish and anticipate clinically important interactions. Accurate use of the compendia could result in withholding needed therapy or needlessly overcomplicating therapeutic decisions. Managing drug therapy means tailoring drug regimens to both avoid significant interactions and minimize the potential for adverse events. A drug interaction is a change in the action or side effects of a drug caused by concomitant administration with a food, beverage, supplement, or another drug. Cause of a drug interaction involves one drug which alters the pharmacokinetics of another drug. Alternatively, drug interactions result from competition for a single receptor or signaling pathway. Both synergy and antagonism occur during different phases of

the interaction between a drug and an organism. For example, when synergy occurs at a cellular receptor level this is termed agonism, and the substances involved are termed agonists. On the other hand, in the case of antagonism, the substances involved are known as antagonists. The risk of a drug-drug interaction increases with the number of drugs used. Over a third (36%) of the elderly in the U.S. regularly uses five or more medications or supplements, and 15% are at risk of a significant drug-drug interaction.

2. METHODOLOGY

Design and study population

This was a cross-sectional retrospective study, carried out by using automated medication records of 280 randomly selected patients who had been admitted to neurology ward and receiving at least two medications. Initially, demographic information of patients such as age, gender, and clinical diagnosis were recorded and incomplete patients' records were excluded from the study.

Limitations of the study

Although there much work remains to be done, and important findings have been generated in this study, it was limited to only those patients admitted in the neurology ward of the hospital. To obtain a clearer picture of the drug-drug interaction, data for out-patients are also needed.

Data collection and screening of Potential drug- drug interactions(pDDIs): The study protocols complied with the guidelines of the Declaration of Helsinki[1, 2] and the ethical committee of hospital for the conduct of this study. In-patient's records were reviewed and screened retrospectively for pDDIs using computerized drug interaction and information system, the Micromedex Drug-Reax System.

The entries of all prescribed drugs to the selected patients from the date of admission till the date of discharge were made. Patients with major severity were screened out. Categorization[3] of clinically potential DDIs was made on basis of Onset, severity and scientific evidence.

Statistical analysis

Data was analyzed statistically by using Graph Pad Prism 5 and the Chi-square test was used to analyze the data and a P value < 0.05 was defined as statistically significant.

3. RESULTS AND DISCUSSION

SOCIO-DEMOGRAPHIC DETAILS OF NEURO SURGERY PATIENTS

Gender distribution

The total number of patients included from the study site during the period based on that inclusion/exclusion criteria was found to be 280 patients, In which male patients were 172 (53.07%) and female patients were 108 (46.09%). The details of the gender distribution were given below in

Table 1 and Figure 1

Table 1: Gender distribution

Gender	No. of patients
Male	172(53.07%)
Female	108 (46.09%)

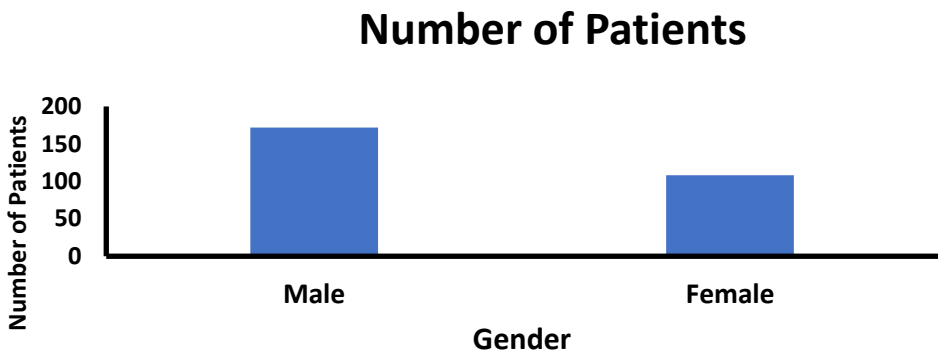

Figure 1: Gender distribution

Age wise distribution

The result of mean age of the study population was found to be 8.1± 3.463 (1.13:1) of the overall study population. Where age between 17-20 years were 20 (7.05 %) and age between 21-39 years were 38 (13.06%) and the age between 40-59 years were 141 (50.02) whereas above the age 60 years were 81(29.01%) the details were given in **Table 2 and Figure 2.**

Table 2: Age wise distribution

Age(yrs)	No. of Patients (%)
≤20	20(7%)
21-39	38(13%)
40-59	141(50%)
≥60	81(29%)

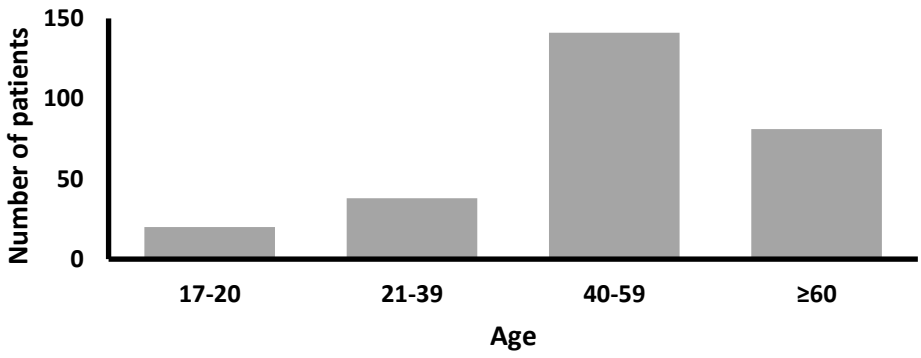

Figure 2: Age wise distribution

NUMBER OF MEDICATIONS IN EACH PRESCRIPTION

Out of 280 patients the medications prescribed for each patient ≤4 medications prescribed to 41 (14%) patients, 5-7 medications prescribed to 82 (30%) ≥8 medication prescribed to 157 (56%) patients

Table 3: Number of medications per patient

No. of medications in each prescription	No. of patients
≤4	41 (14%)
5-7	82 (30%)
≥8	157 (56%)

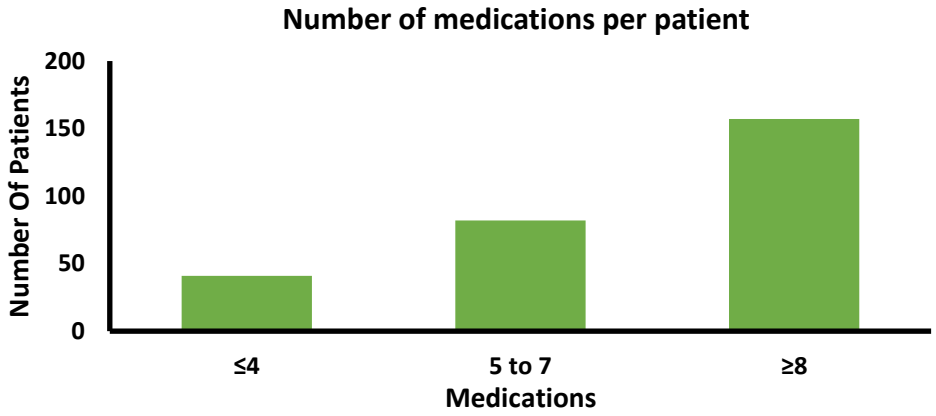

Figure 3: Number of medications per patient

DRUG INTERACTIONS

Among 280 patients of neurosurgical ward 201 patients had the drug-drug interactions and remaining 79 patients were not found any drug-drug interactions

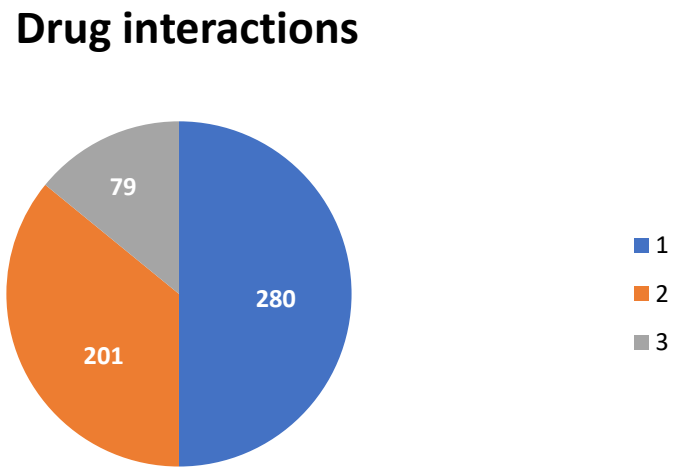

Figure 4: Drug interactions

DOCUMENTATION OF DRUG INTERACTIONS

In total of 638 Drug-Drug interactions some documented and which are categorized as Excellent 84, good 180, fair 310 and some are not documented 64 drug interactions

Table 4: Documentation of interactions

DOCUMENTATION	NO. OF INTERACTIONS
Excellent	84
Good	180
fair	310
Not documented	64

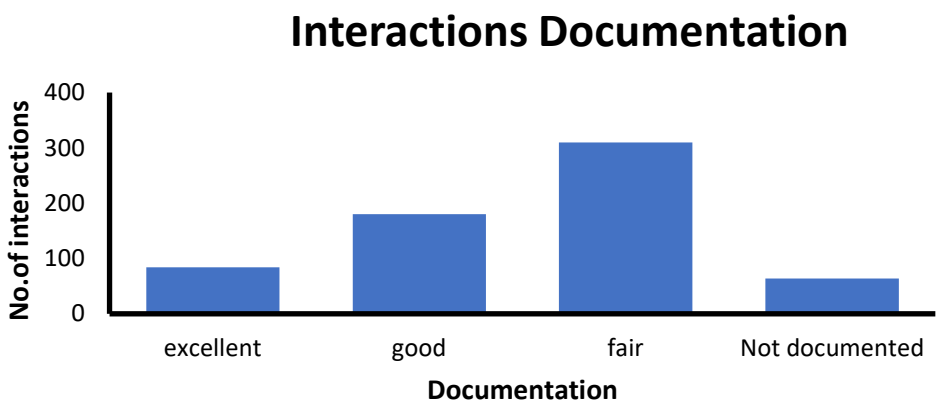

Figure 5: Documentation of interactions

Prevalence of pDDIs

The total number of interactions identified was 638. Out of 280 patients, 201 had at least one pDDIs regardless of type of severity. In 79 patients no interaction was observed.

Levels of pDDIs

The identified pDDIs were categorized on the basis of level of severity, scientific evidence and onset and are given table 5. Among 638 pDDIs, most of were major (399, 62.5 %) or moderate severity (199, 31.01 %); excellent (84, 13.18 %) good (180, 28.21 %) or fair (310, 48.58%) type of scientific evidence; rapid (182, 28.06%) delayed (163, 25.96 %) or non-specified onset (347, 54.38 %)

Table 5: Distribution of identified potential drug-drug interactions on the basis of levels

Level	N	%	X^2	P-Value
Severity				
Contraindicated	26	04.32		
Major	399	62.50	627.836	<0.001
Moderate	199	31.01		
Minor	14	02.01		

Documentation				
Excellent	84	13.18		
Good	180	28.21	127.256	<0.001
Fair	310	48.58		
Onset				
Rapid	182	28.06		
Delayed	163	25.96	83.313	<0.001
Non specified	347	54.38		

Commonly interacting combinations

About 71 interacting pairs were identified in this study. There were top 16 major frequently occurring interacting pairs of pDDIs (Table 6).

Table 6: Identified potential drug-drug interactions and their adverse out comes

Interaction	N	Severity	Onset	Evidence	Potential adverse outcomes
Meropenem+ Valproic acid	58	Major	Rapid	Excellent	Loss of seizure control
Tramadol + Metoclopramide	56	Major	Not specified	Fair	Increase the risk for seizure
Haloperidol+ Tramadol	48	Major	Rapid	Fair	Increase the risk for seizure
Aspirin + Enoxaparin	43	Major	Not Specified	Fair	Increase the risk for bleeding
Clopidogrel+ Enoxaparin	37	Major	Not Specified	Fair	Increase the risk for bleeding
Diazepam+ Phenytoin	32	Major	Not Specified	Good	Results in altered serum phenytoin concentration
Tramadol + Linezolid	22	Major	Not Specified	Good	Increase the risk of Serotonin syndrome
Aspirin + Clopidogrel	19	Major	Not Specified	Fair	Increase the risk of bleeding
Diclofenac + Enoxaparin	17	Major	Not Specified	Good	Increase the risk of bleeding.
Ceftriaxone + Heparin	12	Major	Not specified	Fair	Increase the activity of Heparin
Heparin + Aspirin	10	Major	Not Specified	Fair	Increase the risk of bleeding.
Enoxaparin + Warfarin	10	Major	Not Specified	Fair	Increase the risk of bleeding.

Escitralopram + Tramadol	7	Major	Not Specified	Fair	Increase the risk of seizures, serotonin syndrome, opioid toxicity and increase concentration of tramadol
Ciprofloxacin + + Prochlorperazine	5	Major	Not Specified	Fair	Increased risk of QT interval prolongation.
Valproic Acid + Imepenem	5	Major	Not Specified	Good	Loss of anticonvulsant effect due to decrease valproic acid concentration
Amikacin + Colistimethate	3	Major	Rapid	Fair	Causes Respiratory depression.

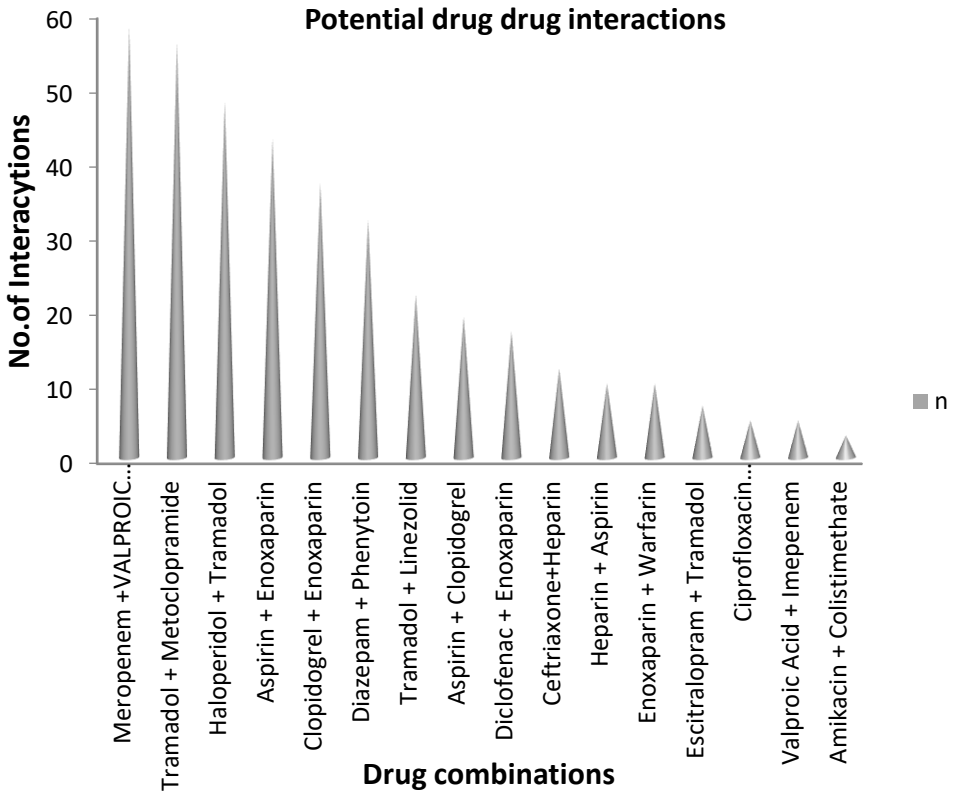

Figure 6: Identified potential drug-drug interactions

This study-represents the importance of computer software program for checking the potential DDIs. About 638 drug interactions were identified from clinical records of 280 hospitalized patients admitted in neurology ward, in which 96% patients showed at least one potential drug- drug interaction during hospitalization regardless of severity of the interaction.

Most of pDDIs were of major severity type (62.2%) and were of serious concern. Medically they are of prime importance for practitioners as they produce negative outcomes. Co-administration with carbapenem antibiotics may substantially decrease-the concentrations of valproic acid in serum.

However simultaneous use of valproic acid with carbapenem is generally not recommended. There is risk of epidural or spinal-hematoma if Aspirin and Enoxaparin combination is used in patients receiving neuraxial-anesthesia or spinal-puncture[4]. While using haloperidol and tramadol combination, one must be cautious, as it can reduce the seizure threshold and thus there is an increased risk of seizures[5]. In our study, the male population shown more drug interactions than the female population, it may be due to the fact that more hospital admissions were seen in male patients. Similar results were obtained in a study[6], and they state it is due to the early detection of common disorders in male patients. However, another study[7] shows that the female population was found with more drug interactions because in their study center more number of female patients was diagnosed with more diseases than males. The study shows that more commonly occurring neurological disorder is a stroke; hypertension is the leading cause of stroke, smoking habit in male patients enhances the risk of stroke in male patients, which is similar to the study[8]. According to our study, most of the patients were of age group between 60 and 70 years. As people get aged, the amount of water in the body decreases as well as the amount of fat tissue relative to water increases. Furthermore, the kidney efficiency to excrete drugs through urine and metabolism by the liver gets decreased. A study reported that the majority of patients were aged above 51 years and were followed by other age groups, whereas, a study[9] reported an age group of 60–70 years. Older people are at high risk of developing an ADR due to PDDI for several reasons. Similarly, the co-administration of diazepam and phenytoin results in phenytoin toxicity[10] .The intake of linzolid with such medicines that results in increased concentrations of serotonin in the central nervous system may lead to Serotonin toxicity[11]. The combination of anticoagulants and NSAID would increase the peri-operative risk of bleeding problems[12].

There are many drug-drug interactions compendia which have been classified on the basis of their levels of severity, onset, evidence based scientific literatures, management-options- or-their-combinations[13-15]

Prevalence of potential drug–drug interactions in this research population was 45.61%. Most of the interactions were major (62.50%) and 31.10% were classified as a moderate interaction. Also noted, patients receiving more than 4 medications have a twofold risk of presenting pDDIs. Results depicted in this study are consistent with several studies conducted in other countries[16-19]. A study reported the prevalence of 45.8% of drug interactions in a study that included 384 pediatric patients in Ethiopia, a figure similar to our work.

This could suggest that regardless of the country and socioeconomic situation, the prevalence of pDDIs is close to 50%. A similar study was also conducted in Mexico. Although both studies included very similar populations and hospital services, they found a higher prevalence than our results. The use of different software to identify pDDIs could explain this difference. In this study, the prevalence of pDDIs was larger than reported by Ismail et al. who found 25.8% prevalence. It is striking that this last author reports a prevalence of 25.8% in a study similar to ours, when most published studies report between 40 and 50%. This difference could be due to the fact that the study was done at a teaching hospital and doctors may be more vigilant in the prescription stage or the doctor in charge of the area may even provide a post-prescription review.

4. SUMMARY AND CONCLUSION

Most interactions presented in our study ranged from major to moderate. Age and polypharmacy were risk factors associated with the appearance of drug-drug interactions. Therefore, identifying and preventing these potentially harmful interactions is a critical component of the clinical pharmacist's

mission. The pharmacist should remain permanently vigilant to the occurrence of these events and suggest adequate therapy adjustments when appropriate. Due to the vulnerable condition of the selected population, careful monitoring is recommended to detect, prevent, and manage potential drug-drug interactions and avoid serious or permanent medical complications. Information provided by this study will help design and implement an action plan that allows timely and effective notification of the most frequent drug interactions as well as sheds light the risk factors associated with their occurrence. Given the importance of the type of population in the study, the active incorporation of the pharmacist as part of the healthcare team could improve the prescribing conditions and thereby favor the patient's health Some of the interactions found were for the benefit of the patient, but others were considered undesirable because they altered the pharmacokinetics of some of the medications administered. Detecting in time the harmful interactions for a patient may favor the patient's safety.

Comparatively high numbers of incidence of pDDIs (major severity) were recorded in the neurology ward of the study site. To avoid the negative consequences of pDDIs, computational software are helpful tools but their successful use is tied to medical experience, knowledge of relevant patient-related factors as well as establishment of drug information centers. The identified pDDIs in this study are of serious nature and are harmful to patients. Therefore, the medication orders should be screened and analyzed by a clinical pharmacist, at least for major DDIs, before the mediation is dispensed. Thereafter, adverse drug reactions should be carefully monitored.

The study highlighted the pDDIs which were high in stroke patients greater than 40 y. pDDIs in prescriptions contained multi-drug therapy is a major concern as such interaction may lead to increased risk of hospitalization and higher health care cost. The majority of interactions were pharmacokinetic in nature, having moderate severity. In this study pDDIs mainly occurred between antihypertensive, anticoagulants and antiplatelet.

The high frequency of pDDIs in patients with neurological problems can have a great clinical relevance, especially when a lot of patients are exposed to pCDDIs which could considerably contribute to serious adverse drug events. The number of prescribed drugs is a significant risk factor for exposure to the pCDDI, so each new drug must be added to therapy with special caution.

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