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Prevalence of potenial drug-drug interactions among psychitric patients in Ayder referral hospital, Mekelle, Tigray, Ethiopia

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Abstract

Introduction: A clinically relevant drug-drug occurs when the effectiveness or toxicity of one medication is altered by the administration of another medicine. Potential Drug-drug interactions are an important cause of adverse drug reactions. Psychiatric patients are increasingly susceptible to drug interactions due to the polypharmacy, nature of the prescribed drugs and most of the drugs prescribed are either enzyme inhibitor or inducers. Objective: To determine the prevalence of the potential drug-drug interactions**. Methodology:** A retrospective cross sectional study was performed from to March to June, 2013. Medications on patients' medical charts were reviewed and analyzed for potential drug-drug interactions based on Micromedex Online Drug Reference. **Results:** In our study, total of 463 potential drug-drug interactions were identified, with median number of one potential drug-drug interaction per patient. Overall 81.65 % of the patients had at least one potential drug-drug interaction; 49.5 % patients had at least one major; and 52.3 % had at least one moderate potential drug-drug interactions. The most frequent potential drug-drug interactions identified were Haloperidol-Trihexphenidyl 74 times and Chlorpromazine–Haloperidol 36 times. **Conclusion:** A high prevalence of potential drug-drug interaction is recorded in our study area. Most potential drug-drug interactions recorded in this stud may cause cardio toxicity and QT prolongation. Patients with the risk of cardiovascular comorbidities and those who are prescribed multiple medications need to be monitored more closely.

Keywords: Potential, Drug interactions, Severity.

Introduction

Drug interactions occur when the effect and/or concentration of a drug is modified by another substance, including a concomitant treatment, over-the-counter medication, food, alcohol, or tobacco.[1] A drug-drug interaction is defined as the pharmacological or clinical response to the administration or co-exposure of a drug with another drug that modifies the patient's response to the drug index.[2]

A clinically relevant drug-drug interaction occurs when the effectiveness or toxicity of one medication is altered by the administration of another medicine or a substance that is administered for medical purposes (to be distinguished from drug-food interactions). Adverse consequences of drug-drug interactions may result from either diminished therapeutic effect or toxicity.[3]

Drug-drug interactions are increasingly an important cause of Adverse Drug Reactions. It is reported that 20-30% of all adverse reactions to drugs are caused by interactions between drugs. This incidence increases among the elderly and patients who take two or more medications (1). Older people are at risk of adverse drug interactions because of high rates of physical comorbidities, and hence increased risk of polypharmacy, as well as age-related changes in pharmacokinetics within this group. The elderly psychiatric populations are particularly prone to be on a number of drugs, including psychotropics, which increases the potential of a harmful drug-drug interaction.[4]

Drugs for psychiatric disorders result in serum concentration changes are generally most relevant for drugs with a narrow therapeutic index such as lithium and clozapine, where increases or decreases play a role in worsening clinical condition or increasing the risk of serious adverse effects.[5]

The most serious interactions with psychotropics result in profound sedation, central nervous system toxicity, large changes in blood pressure, ventricular arrhythmias, and an increased risk of dangerous side-effects or a decreased therapeutic effect of one of the interacting drugs.[6] It is difficult to completely prevent drug-drug interactions especially in patients with psychiatric problems due to the lifelong treatment; use of multidrug regimens and most patients are elderly. Therefore, drug-drug interactions are among the major challenges in psychiatric patients. Monitoring and reporting of drug-drug interactions in medications used for psychiatric problems is necessary due to the pharmacokinetic and pharmacodynamic nature of the drugs. But, in Ethiopia it is uncommon to monitor and report drug-drug interactions. To the investigator's knowledge, there are no studies conducted in Ethiopia concerning drug-drug interactions in patients with psychiatric problems. Therefore, this study was conducted to determine the prevalence of potential drug-drug interactions in patients in psychiatric patients of Ayder referral hospital.

Statement of the Problem

Drug interactions can lead to alteration of therapeutic response or increase untoward effects of many drugs. This can contribute to drug induced illnesses that may result in hospitalizations and deaths.[7] Drug-drug interactions in patients receiving multi-drug therapy are of wide concern. Such interactions are an important cause of adverse drug reactions and may lead to an increased risk of hospitalization and higher health care costs.[8] Prevalence of potential drug-drug interactions in hospital settings has been estimated in some studies to be in the range of 27.8 to 51.4 %.[7]

The risk of unintended and untoward drug-drug interaction is increasing in concert with both the increasing number of pharmaceuticals available and the number of patients on multiple medications.[9] Patients with psychiatric disease are at increased risk relative to other age-matched patients for being on multiple medications and complex regimens, which makes them particularly vulnerable to drug interactions and their untoward effects.[10]

Drug-drug interactions are an especially important issue in psychiatry; because many of the psychotropic agents are CYP 450 inducers or inhibitors that may affect the blood levels of other drugs. Similarly, many of the non-psychotropic drugs that our patients take can significantly increase or decrease the blood levels of most psychotropic agents. To treat patients in a competent and safe manner, some awareness of the drug-drug interaction issue and some means of detecting.[11]

Antipsychotic polypharmacy is a common practice that persists despite a lack of supporting evidence and despite treatment guidelines that discourage it. Polypharmacy raises concerns about increases in total dosages, side effects, and mortality, as well as decreased adherence. It remains a prevalent practice with estimates of antipsychotic polypharmacy among individuals with schizophrenia typically ranging from 10% to 30%. Moreover, the rate of polypharmacy appears to be increasing over time. A study of Medicaid claims for more than 30,000 Medicaid recipients with schizophrenia reported an increase from 32% in 1998 to 41% in 2000.[12] A small scale cross-sectional survey (n = 48), conducted in elderly psychiatric wards identified a total of 152 potential drug-drug interactions in 96 % (46/48) of prescriptions.[7]

The most serious interactions with psychotropics result in profound sedation, central nervous system toxicity, large changes in blood pressure, ventricular arrhythmias, and an increased risk of dangerous side-effects or a decreased therapeutic effect of one of the interacting drugs.[6] Potential drug interaction not only presents a danger to the patients but they can also greatly increase health care costs.[13]

Old age, taking increased number of medications, long hospital stay, gender and comorbid conditions have been reported as common risk factors for drug-drug interactions.[12] In addition to these, other risk factors for drug interactions are malnutrition, malabsorption, chronic liver disease (including liver metastasis), and impaired renal function.[2]

Unfortunately, clinicians frequently miss the occurrence of a drug-drug interaction. Depending on the type of interaction, the effects may build gradually over 1 or 2 weeks and then result in a sign or symptom that could be interpreted as an accentuation of the adverse effects of the drug itself. Thus, often the clinician perceives that the drug is causing the symptom, while the blood levels of the "offending" drug are increasing.[1]

Studies are needed to explore the overall pattern of potential drug-drug interactions in psychiatric patients along with their levels and correlation with different risk factors. Data on prevalence of drug interactions in psychiatric patients in our hospital and also in Ethiopia is not available. Therefore undergoing this study could help in filling this gap and rationalizing pattern on the site.

Objectives

General objectives

- To determine the prevalence of the potential drug-drug interactions in psychiatric patients of ARH, Mekelle, Tigray, Ethiopia.

Specific objectives

- To determine the prevalence of potential drug-drug interactions in psychiatric patients.
- To identify the type of drugs involved in potential drug interactions in psychiatry patients.

Methodlogy

The study was conducted from April to June, 2013 in Ayder referral Hospital situated in Mekelle city, Tigray, Ethiopia. Mekelle is a capital city of Tigray region and found 783kilometers far from Addis Ababa. Ayder referral hospital serves for about one million people. It has 472 beds and it provides services to patients from the region and the neighboring region of Afar and Amhara. The Hospital has a psychiatric outpatient and inpatient units which were established in August 2009. The clinic operates with two psychiatrist, 7 psychiatric nurses and 4 clinical nurses five days a week.

Institutional based retrospective cross sectional study was performed. The study population was medical records of patients with psychiatric illness in psychiatric unit of Ayder referral hospital. The sample size was determined by the assumption that 50% of psychiatric patients may experience drug interaction with 5% marginal error and 95% CI (α=0.05). Based on this assumption, the actual sample size for the study was determined using the formula for single population proportion. 240 patient medical records were included in the study. A systematic sampling technique with sampling interval of 6 was employed to reach the study sample. every sixth patient's medical records was included in the study until the allocated number of study subjects was reached. If the selected patient was not illegible, the next number to the sampling interval was taken to be included. Based on the patients'

medication recording number a starting patient was determined by lottery method.

A data collection format, designed to collect patient demographic information, number of drugs prescribed, comorbidities and drugs for psychiatric illnesses was used in the data collection.

All medications that were prescribed to the patients were screened for potential drud-drug interactios. Micromedex 2.0 Drug-Reax® System (Thomson Reuters Healthcare Inc., Greenwood Village, Colorado, USA) was used to screen and classify potential drug-drug interactions. The data on drug-drug interactions identified was documented. Potential drug-drug interactions 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 hours, i.e., days to week(s).
- **Unspecified**: The occurrence of effect of interaction is not specified.

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 report.

The collected data were cleaned, coded and fed into SPSS for Windows version 16 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics was conducted for detecting inconsistencies, missing values and to determine prevalence.

Result

General patient characteristics

Of the total 240 patients' medical records, 34 were excluded due to incomplete information, and age less than 15 years of age. While 216 were reviewed for potential drug-drug interactions. In this Study among the 216 patients, 116 (53.48 %) were male and 100 (46.52 %) were female; median age was 27 years; and median number of prescribed medications was 3.81 (Table 1).

Table 1: General patient characteristic

Variables		Sex	
		Male, n (%)	Female, n (%)
Age	15-30	82 (38)	61(28.2)
	31-45	26 (12)	29 (13.4)
	46-60	4(1.9)	8 (3.7)
	>60	4(1.9)	2 (0.9)
	Total	116 (53)	100 (46.3)
Number of prescribed medications per patient	2 – 3	63 (29.2)	58 (26.9)
	4-6	43 (19.9)	30 (13.9)
	7 – 9	7 (3.2)	9 (4.2)
	> 9	3 (1.4)	3(1.4)
	Total	116 (53.7)	100 (46.3)
Standard deviation		2.26	
Range		2-21	

The most common psychiatric illness observed in patients participated in the study was schizophrenia. It was encountered in 123 (57%) patients while depression and bipolar disorders were estimated to account 62(28.7%) and 27(12.5%) respectively. Among the total patients 43 (20%) were with more than one psychiatric illness (table 2).

Table 2: prevalence of most common psychiatric illness

Type of psychiatric illness	Frequency, n (%)
Schizophrenia.	123 (57)
Depression	62(28.7)
Bipolar disorders	27(12.5)
Anxiety	15(7)
Delusional disorders	6(2.8)
Others	20(9.2)

This study also assessed the comorbidities encountered with the patients to which medications other than psycotropics were prescribed. Patients with at least one comorbid conditions were 137(63.4%). Extra pyramidal side effects were the commonest comorbid condition, while the other comorbidities were generalized in to infectious (38, 17.6%), non infectious (14, 6.5%), GI (14, 6.5%), and neurological problems (13, 6%). Patients with more than one non psychiatric comorbidities were 37(17.13%)

Prevalence of potential drug-drug interactions

One hundred seventy six (81.8 %) patients had at least one potential drug-drug interaction regardless of type of severity; 112 (52.2 %) and 118 (54.9 %) patients had at least one potential drug-drug interaction of major and moderate severity, respectively. Contraindications and minor types of potential drug-drug interactions were less prevalent making 13(6.02 %) and 22 (10.2 %). In around half of the cases, 1–2 potential drug-drug interactions per patients were identified with median of 1 potential drug-drug interactions (Table 3).

Table 3: prevalence of potential drug-drug interactions

Number of potential drug-drug interactions per patient		Frequency n (%)		Total
	1-3	61 (34.7)	73 (41.5	134 (76.1)
	4-6	12 (6.9)	20 (11.3	32 (18.2)
	7 – 9	2 (1.1)	5 (2.8	7 (3.9)
	>9	3(1.7)	0	3 (1.7)
	Total	78 (44.3)	98 (55.7)	176 (100)
	Standard deviation			2.66
	Range			0 – 23

Levels of potential drug-drug interactions

The identified potential drug-drug interactions were categorized into different levels according to onset, severity and scientific evidence. Among the 463 potential drug-drug interactions identified, most were of moderate 232 (50.1%) or major severity 198 (42.8%). Of the total potential drug-drug interactions 13 (2.8%) were with contraindication and 22(4.7%) with minor severity. Based on the type of scientific evidence 4(0.8%) were with excellent documentation, 223 (48.2 %) good and 236(50 %) fair. On assessing the onset of the potential drug-drug interaction (14,3%) were with rapid onset, (223, 48.2%) delayed onset and (226,48.8%) were with non-specified onset (Table 4).

Table 4: level of potential drug-drug interaction

Level	Frequency of potential drug-drug interactions *n(%)*
Severity	
Contraindicated	13 (2.8)
Major	198 (42.8)
Moderate	232 (50.1)
Minor	22 (4.7)
Documentation	
Excellent	4(0.8)
Good	223 (48.2)
Fair	236 (51.0)
Onset	
Rapid	14 (3)
Delayed	223 (48. 2)
Not specified	226 (48.8)

Common interacting combinations

Table 5 showed common interacting drug combination along with their frequency. Haloperidol, Chlorpromazine, trihexyphenidyl, fluphenazine Decanoate, Trifluoperazine, Amitriptyline, Fluoxetine, trihexyphenidyl, diazepam and carbamazepine were the drugs most commonly encountered in these potential drug-drug interactions.

Table 5: Common interacting drug-combinations

Interaction	Frequency
Contraindicated	
Chlorpromazine – Thioridazine	4
Major	
Chlorpromazine – Haloperidol	36
Chlorpromazine – Amitriptyline	14
Amitriptyline – Fluoxetine	14
Moderate	
Haloperidol - Trihexphenidyl	74
Chlorpromazine - Trihexphenidyl	30
Fluphenazine Decanoate - Trihexphenidyl	29
Trifluoperazine - Trihexphenidyl	9
Trifluoperazine - Haloperidol	9
Minor	
Fluoxetine – Diazepam	9

Discussion

In the current study it was found that 176 (81.8 %) patients had at least one potential drug-drug interactions. This was higher when compared with another study done in Pakistan on psychiatric ward which was 64.7%.[7] This discrepancy in prevalence may be a result of high utilization of drugs having more interacting potentials (e.g., haloperidol, fluphenazine, trihexyphenidyl, Chlorpromazine, Amitriptyline and fluoxetine) in our set up. It was also lower when compared to a study on elderly psychiatric patients by Vasudev and Harrison which was 96%.[4] This may be largely due to elderly patients are prone to potential drug-drug interactions because of physiologic changes, higher vulnerability to other comorbid conditions and polypharmacy. Our finding is lower when compared to other wards such as the oncology (27%) [3], Pneumology(45%) [14], Intensive care unit (70%) [15] and pediatrics (66%) [16]. This confirms that psychiatric patients have higher exposure to potential drug-drug interactions than patients in any other wards.

Our finding showed that the recorded median number of potential drug-drug interaction was 1 per patient which is consistent with the studies done in Psychiatry and pulmonology wards.[7,14] The recorded average number of prescribed medications in our study was found to be 3.81(±2.26). This is slightly higher when compared to studies by Ismail M, et al. (1.98).[7] But it was lower when compared to the study done on cancer patients in Canada where the average prescribed medications were 5 drugs per patient.[17]

Our finding on prevalence of potential drug-drug interactions of major severity (42.8%) was higher compared to other studies. Vasudev and Harrison reported the major severity to be 27.2% [4], while a study by Jain T. *et al*. on HIV patients reported 15.2% [10]. Contraindicated potential drug-drug interactions account 2%, which was slightly lower than a study done by Vasudev and Harrison (2.4 %).[4] The prevalence of moderate potential drug-drug interaction was 50.1% which is lower than the study done by Vasudev and Harrison (75.6 %).[4] This discrepancy may be due to the reason that their study was done in elderly psychiatric patients which are susceptible to comorbid conditions; Polypharmacy is common in elderly psychiatric patients and the sample size of the study was very small (48 patients). In our study Minor severity potential drug-drug interactions contributed 4.7% out of all potential drug-drug interactions which is slightly higher than Vasudev and Harrison study (3%).

The current study showed that delayed onset was contributed 48.2% of all the identified potential drug-drug interactions. This finding is lower than a study done in psychiatric patients in Pakistan (71%) and 70% of study in pulmonology ward, in the same country respectively.[7,14] The potential drug-drug interaction with rapid onset was found to be 3% which is far lower than studies done in Pakistan 29% in the psychiatry ward and 30% in the pneumology ward in Pakistan.[7,14] The rest 48% were with non-specified onset. This finding was much higher when compared to study done in India on HIV patients (13.8%).[16] This discrepancy could be due to the use of Psychotropic drugs for which most drugs used for the psychiatric illness are with enzyme inducing activity. This takes relatively longer time for the potential drug-drug interactions to occur.

In our study potential drug-drug interactions with good scientific evidence was found to be 51.0%.This result is higher when compared to the study done in the pneumology ward (16.3%). In this study the potential drug-drug interactions with excellent scientific evidence accounts 0.8%, which is lower compared to the study in Pakistan (4.6%).[16]

Conclusion

The prevalence of potential drug-drug interactions reported in the psychiatric ward was 81.8%, a majority of which were of moderate and major severity. Drug interactions of contraindicated and major severity and potential drug-drug interactions with excellent and good clinical evidence must be clinically studied. Haloperidol, Chlorpromazine, trihexyphenidyl, fluphenazine Decanoate, Trifluoperazine, Amitriptyline, Fluoxetine, trihexyphenidyl, diazepam and carbamazepine were the drugs most commonly encountered in these potential drug-drug interactions.

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