Original Research

ASSESSING THE PREVALENCE AND SEVERITY OF POTENTIAL DRUG-DRUG INTERACTIONS AMONG MENTALLY ILL INPATIENTS.

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Submitted on: 14.02.2016 Revised On: 18.02.2016 Accepted on: 22.02.2016

ABSTRACT

Mental health refers to a wider range of activities directly or indirectly related to the mental well-being. Mentally ill patients in Kenya are increasingly becoming prone to a high risk of polypharmacy, complex therapeutic regimen and frequent modification of therapy. The objective of this study was to assess the prevalence and severity of potential drug-drug interactions among mentally ill patients admitted at Mathari Mental Hospital in Nairobi County, Kenya. The study was designed in a retrospective descriptive cross-sectional study of medical records data of patients who had undergone mental treatment and were admitted at Mathari Mental Hospital between July and December 2013. This study focused on a population comprising of all mentally ill patients who were admitted and put on medication during the study period of either gender and ageing between 13 to 75 years. One hundred and seventy five patient files were sampled, married and unemployed patients had a statistically significant ($p<0.05$) association with a prevalence and severity of potentially serious drug interactions. Participants with bipolar mood disorder had a statistically significant association with potentially serious drug interactions [OR 4.39 CI (1.09, 17.46) p = 0.04]. There was a statistically significant association of potentially serious drug interactions with fluphenazine [OR 10.38 CI (4.66, 23.10) $p<0.01$) haloperidol [OR 4.39 CI (2.29, 8.41) $p<0.01$] and amitriptyline [OR 3.39 CI (1.36, 8.41) $p=0.01$]. Married, unemployed and patients on fluphenazine, haloperidol, amitriptyline and chlorpromazine were at a higher risk of having potentially serious drug-drug interactions. These drugs exhibited both pharmacodynamic and pharmacokinetic drug interaction mechanisms. We recommend continuous electrocardiogram for patients on specific antipsychotics like haloperidol.

KEY WORDS : Mental Health, Drug Interaction, Prescriptions.

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Indian Research Journal of Pharmacy and Science; 8(2016) 331-343;
Journal home page: https://www.irjps.in

INTRODUCTION

Mental health refers to a wider range of behavioral activities directly or indirectly related to the psychological well-being of an individual. The World Health Organisation (WHO) defines health as: "A state of complete physical, mental and social well being, and not merely the absence of disease". Mental health is thus a state of well-being that encompasses the prevention of mental disorders and treatment and rehabilitation of people affected by mental disorders [1].

In most cases, care providers for mentally ill patients encounter clinical situations which require medications. These clinical situations require familiarity with a broad category of these medications. It includes the basic understanding of indications, adverse effects and drug-drug interactions. In particular, it is very important to recognize the many potential interactions associated with cytochrome P450 metabolism, which is common to many psychotropics and other central nervous system (CNS) drugs [2]. Mentally ill patients have a high risk of polypharmacy hence increase in the likelihood of drug-drug interactions. This may cause partial or complete abolishment of treatment efficacy, thus underlining the importance of understanding the potential drug-drug interactions and the adverse drug reactions associated with them [3].

Potential drug-drug interactions are based on the risk-benefit evaluation of a medicinal product and incidences of adverse events, reduced efficacy or increased toxicity which are often predictable, avoidable or manageable [4]. This risk benefit evaluation 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. Results from different studies have estimated the prevalence of hospital admissions due to drug-drug interactions to be between 1 % to 21 % (an average of 11 %) [5-6]

Studies are needed to explore the overall pattern of potential drug-drug interactions (pDDIs) in psychiatric patients along with their levels and correlation with different risk factors. Hence the main aim of this study was to determine the prevalence and severity associated with pDDIs in hospitalized mentally ill patients in Mathari Mental Hospital.

LITERATURE REVIEW

Drug-drug interactions

A drug-drug interaction is defined as a pharmacological 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[7]. There two main mechanisms of interactions, pharmacodynamic or pharmacokinetic. Pharmacodynamic drug interaction occurs when one drug modulates the pharmacologic effect of another by additive, synergistic or antagonistic effect. It is occurs in drugs which compete with each other at the pharmacological target and/or have similar or opposing pharmacodynamic effects. In pharmacokinetic interactions, one drug alters the concentration of another drug by altering its absorption, distribution, metabolism or excretion. Pharmacokinetic

interactions occur if there are indications that the interaction profile may not be adequately predicted from and *in vivo* interaction data for the separate drugs [8, 9].

Pharmacokinetic interactions of psychotropic drugs

Most psychotropic drugs exhibit the two types of pharmacokinetic drug interaction mechanisms.

Metabolism and Distribution

Drugs compete for binding sites differently, protein-binding interactions may be significant for drugs with a small volume of distribution or where a temporary increase in plasma may result in unacceptable adverse effect and includes drugs like phenytoin. Most psychotropics are protein bond to a certain extent with the exception of lithium and gabapentin [8, 9].

Metabolic drug interactions involve, enzyme induction or inhibition, which may affect the substrate drug and their plasma levels. This is exhibited when carbamazepine and quetiapine are used together, carbamazepine decreases the effect of quetiapine by affecting hepatic enzyme CYP 3A4 [10]. Metabolic drug interactions are also significant for drugs with low ratio between a therapeutic and toxic dose, notable drugs include phenytoin and theophyline [11].

Many psychotropic drugs interact with each other in this manner since most are metabolised in the liver by Cytochrome P450 and may therefore cause inhibition or induction of enzyme Cytochrome P450 resulting in increased or decreased effect [12, 13]. Table 2.1 outlines the common psychotropic drugs that are substrates, inhibitors and inducers of CYP450 isoenzyme.

Pharmacodynamic interactions

The most commonly encountered interactions in practice are pharmacodynamic interactions. Clinically significant pharmacodynamic drug interactions with psychotropic drugs are based on antagonistic, additive or synergistic drug interactions.

Antagonistic interactions

Antipsychotropics that are potent dopamine D2 antagonists oppose the effect of dopamine agonists in management of Parkinson's disease. When used together, the therapeutic effect of both drugs will be diminished [14]. Drugs with anticholinergic properties can pharmacodynamically oppose the effects of anticholinesterase drugs used in Alzheimer's disease. Cyproheptadine antagonizes postsynaptic serotonin receptors hence concomitant use of cyproheptadine with drugs that possess serotonin-enhancing properties might be expected to result in a pharmacodynamic interaction. Reduction in antidepressant efficacy has been reported when cyproheptadine was administered concurrently with fluoxetine and paroxetine [15].

Table 1: Psychotropic drugs that are substrates, inhibitors and inducers of CYP 450 isoenzymes

CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP2D6	CYP3A4,5,7
Substrates					
Amitriptyline Chlorpromazine Clomipramine Clozapine Fluvoxamine Haloperidol Imipramine Methadone Olanzapine	Bupropion Methadone	Amitriptyline Citalopram Clomipramine Diazepam Imipramine Moclobemide Phenobarbitone	Amitriptyline Fluoxetine Phenytoin	Amitriptyline Amphetamine Chlorpromazine Clomipramine Desipramine, Donepezil, Fluoxetine, Fluvoxamine Galantamine, Haloperidol Imipramine, Nortriptyline Olanzapine, Paroxetine Risperidone, Sertraline Zuclopenthixol	Alprazolam, Amitriptyline Carbamazepine Clomipramine Clonazepam, Clozapine Diazepam, Donepezil Haloperidol Imipramine, Methadone Midazolam, Mirtazapine Pimozide, Quetiapine Triazolam
Inhibitors					
Fluvoxamine		Fluoxetine Fluvoxamine Modafinil Paroxetine Valproate	Fluoxetine Fluvoxamine Paroxetine	Bupropion Chlorpromazine Doxepin, Duloxetine Fluoxetine Haloperidol, Methadone Moclobemide, Paroxetine Reboxetine, Sertraline Thioridazine, Valproate	Fluoxetine, Fluvoxamine Valproate
Inducers					
Barbiturates,	Phenobarbitone Modafinil	Carbamazepine	Barbiturates		Carbamazepine Modafanil, Phenytoin

Additive pharmacodynamic interactions

Additive pharmacodynamic interactions involving psychotropic drugs resulting in various forms of adverse reactions are; over sedation, seizures, serotonin syndrome, hypertension, anticholinergic effects, hypotension, QTC prolongation and hematological effects.

Over sedation due to the additive effects of drugs with sedative properties is often encountered when psychotropic drugs like chlorpromazine and fluphenazine are combined. Over sedation may also occur as the result of inhibition of metabolism of the sedating drug through CYP450 metabolism [16].

Concurrent use of lithium and antipsychotic drugs or carbamazepine may result in neurotoxicity characterized by weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brain damage. This interaction is rare and is more likely to occur with higher plasma levels of lithium [17].

Seizures may result from the additive effects of two or more drugs that lower the seizure threshold. Most antipsychotic drugs and antidepressants can reduce the seizure threshold. Antipsychotics such clozapine and chlorpromazine have the greatest epileptogenic potential whereas among the antidepressants, the tricyclic antidepressants (TCAs) pose the greatest risk.

Patients that require a combination of drugs that reduce the seizure threshold should be maintained on the lowest effective dose, with careful introduction and withdrawal of high-risk drugs [18].

Serotonin syndrome can occur with one or more serotonergic drugs. Serotonin syndrome is a potentially life threatening condition characterized by mental state changes, myoclonus, tremor, hyper reflexia, fever, sweating, shivering and diarrhoea. All of the antidepressants, except reboxetine, can contribute to serotonin syndrome and there is a greater risk of serotonin syndrome with combinations of selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) or SSRIs and serotonergic TCAs (clomipramine, amitriptyline, and imipramine). Other drugs such as opioids (tramadol, pethidine, and dextromethorphan), stimulants (phentermine, diethylpropion, amphetamines, and sibutramine), $5HT_1$ agonists (sumatriptan, naratriptan, and zolmitriptan) and others (illicit drugs, selegiline, trytophan, buspirone, lithium, linezolid and St John's wort) can also contribute to serotonin syndrome. Combined use of serotonergic drugs should be avoided or monitored carefully [19].

The concomitant use of MAOIs and tyramine containing food, or drugs that increase the level of monoamines (serotonin, noradrenaline, or dopamine) can result in interactions that have the potential to cause hypertensive condition. Combinations of monoamine oxidase inhibitors (MAOIs) and these drugs are contraindicated. The severity and consequences of such interactions may vary among individuals. If substantial and rapid increases in blood pressure (an increase of 30 mm Hg or more in systolic blood pressure within 20 minutes) occur, patients may experience symptoms associated with subarachnoid haemorrhage or cardiac failure [20].

Caution should be taken when combining drugs with anticholinergic properties like alprazolam, amitriptyline, diazepam and flurazepam due to enhanced anticholinergic effects such as dry mouth, urinary retention and constipation. There is also an increased risk of developing paralytic ileus, or central anticholinergic delirium characterised by cognitive changes as well as symptoms such as dry skin, dry mucous membranes, dilated pupils, tachycardia and absence of bowel sounds [21].

Caution should be taken when combining drugs with an antihypertensive effect. Hypotension is a common adverse effect of many psychotropic drugs due to alpha-adrenergic blockade common with prazosin, doxazosin and phenoxybenzamine. Hypotension is a dose related and additive adverse effect that is a

potentially serious due to the risk of falls, cerebral ischaemia or myocardial ischaemia [22].

Many psychotropic drugs including certain antidepressants, antipsychotics and lithium have been associated with lengthening of the cardiac QTC interval, which increases the risk of ventricular arrhythmias such as torsades de pointes. Psychotropic drugs with the greatest effect on QTC interval include chlorpromazine, haloperidol, doperidol, pimozide and thioridazine. The risk of cardiac arrhythmia and sudden death may be increased further when these drugs are used concomitantly with other QTC prolonging drugs like astemizole, cisapride, erythromycin and sotalol. QTC prolongation is a dose dependent effect; hence inhibition of drug metabolism is also an important interaction to consider. Indirect pharmacodynamic interactions with psychotropic drugs that prolong the QTC interval should also be considered. These interactions involve drugs that affect the electrolyte balance or that cause bradycardia, thereby increasing the risk of arrhythmia [23, 24].

Psychotropic drug-induced haematological effects are rare however, additive drug effects are noted on white blood cells and platelets among patients on clozapine and drugs known to be myelosupressive. Due to the risk of agranulocytosis, these combinations are contraindicated. Many other psychotropic drugs have also been associated with agranulocytosis, most notable drugs are carbamazepine and the phenothiazines. Serotonergic drugs and valproate can affect platelet function.

SSRIs can inhibit serotonin reuptake into the platelets, reducing platelet's ability to aggregate. When SSRIs are used in combination with NSAIDs or anticoagulants the risk of bleeding may increase although this interaction is usually uneventful. Sodium valproate can inhibit the second stage of platelet aggregation and increase bleeding time. Caution is required when valproate is used with other drugs that affect coagulation or platelet function [25, 26].

Data analysis

Data was collected, coded and entered into computer excel database where data analysis was done in three steps namely descriptive analysis, bivariate analysis and multivariate analysis.

Descriptive statistical analysis described the outcomes in patient demographic factors using percentages or frequency for categorical variables. In continuous variables like age the mean and standard deviation was used to describe the distribution.

Bivariate analysis compared the outcomes and predictor variable using logistic regression analysis where odds ratio with 95 % confidence intervals (95 % CI) were calculated and probability (p) values of 0.05 or less were considered to be statistically significant.

A multivariate analysis of a parsimonious forward stepwise model building was done to determine the drugs with best predictor variables for potentially serious drug-drug interactions. All statistical analyses were done out using Stata® 10.0 version statistical software.

RESULTS

Drugs prescribed to study participants

Forty-six different drugs were prescribed, the average number of drugs per prescription was found to be 6.5. these drugs included psychotropic drugs 18 (39 %), antihypertensives 7 (15 %), analgesics 6 (13 %), anti-retrovirals 4 (9 %), anti-tuberculosis 4 (9 %), antibiotics 1 (2 %) and other drugs 6 (13 %). Figure 1 shows the classification of prescribed drugs.

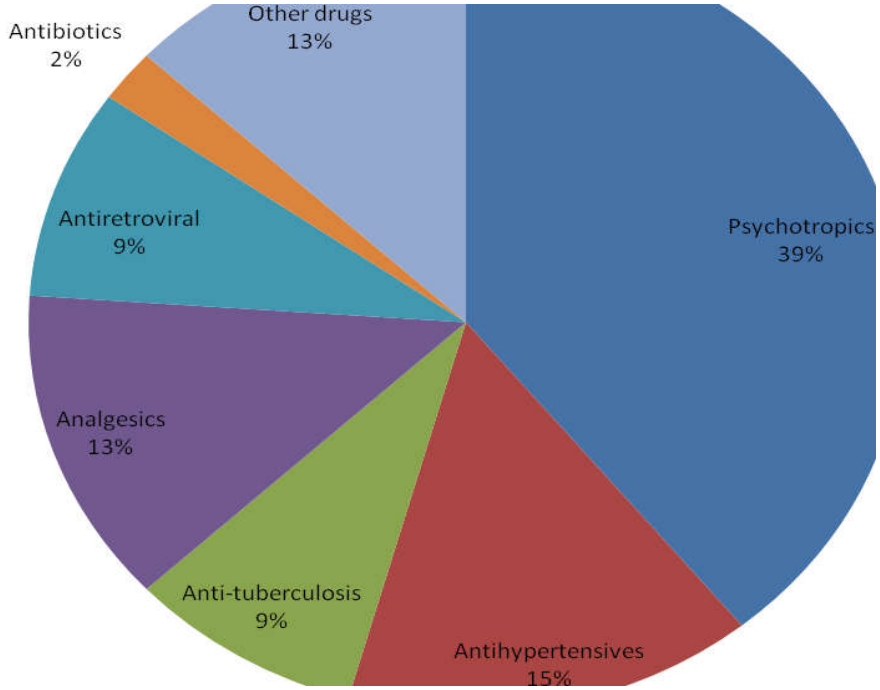

Figure 1: Classification of prescribed drugs

Mental diseases associated with serious drug interactions

Most of the patients with serious drug interactions were diagnosed with bipolar mood disorder 33 (18 %), and had a statistically significant association [OR 4.39(1.09,19.64) p=0.04] with potentially serious drug-drug interactions as shown in Table 2.

Table 2: Association between mental diseases with serious drug interactions

Mental diagnosis	(n=175) Patients	Serious (n=72) (%)	Not-Serious (n=103) (%)	OR (95% CI)	p-value*
Bipolar mood disorder	58	33 (45.8)	25 (24.3)	4.39(1.09,17.64)	**0.04**
Schizophrenia	48	26 (36.1)	22 (21.3)	3.94(0.96,16.12)	0.06
Substance abuse disorder	10	5 (6.9)	5 (4.9)	3.32(0.55,19.89)	0.19
Unipolar disorder	13	3 (4.2)	10 (9.7)	_	_
Alcohol use disorder	15	3 (4.2)	12 (11.7)	0.84(0.14,5.05)	0.84
Epilepsy	20	1 (1.4)	19 (18.4)	0.18(0.02,1.92)	1.15
Alzheimer and dementia	11	1 (1.4)	10 (9.7)	0.33(0.03,3.78)	0.38

*Significant p values are in **bold**

Severity of potential drug-drug interactions

There were 151 (30 %) incidents in which psychotropic drugs were involved in potentially serious drug-drug interactions, potentially significant drug-drug interactions accounted for most of the interactions at 262 (52 %) while minor drug-drug interactions were at 72 (14 %) and 21 (4 %) had no drug-drug interactions as outlined in Figure 2.

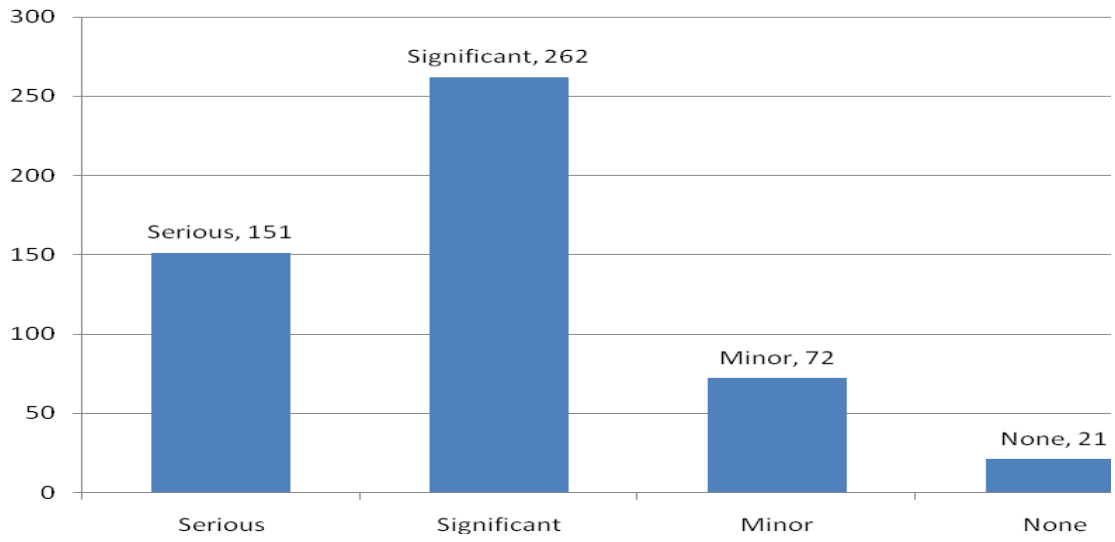

Figure 2: Severity of potential drug-drug interactions

Among the psychotropic drugs most potentially serious drug-drug interactions were attributed to haloperidol (28.5 %) and fluphenazine (25.2 %) use. Potentially significant drug interactions were attributed to carbamazepine (25.6 %) and benzhexol (27.5 %) use while most minor drug interactions were due to carbamazepine related drug interactions at (28.6 %) as shown in Table 3.

Table 3: Psychotropic drugs and severity of potential drug interactions

Drug	Serious (n=151) (%)	Significant (n=262) (%)	Minor (n=72) (%)	None (n=21)(%)
Haloperidol	43 (28.5)	21 (8.0)	4 (5.6)	1 (4.8)
fluphenazine	38 (25.2)	7 (2.6)	3 (4.2)	0 (0.0)
Chlorpromazine	21 (13.9)	19 (7.3)	1 (1.4)	0 (0.0)
Amitriptyline	16 (10.6)	6 (2.3)	1 (1.4)	1 (4.8)
Carbamazepine	13 (8.6)	67 (25.6)	28 (38.9)	6 (28.6)
Diazepam	8 (5.3)	6 (2.3)	0 (0.0)	0 (0.0)
Fluoxetine	5 (3.3)	3 (1.1)	5 (6.9)	1 (4.8)
Risperidone	3 (2.0)	8 (3.1)	4 (5.6)	1 (4.8)
Benzhexol	2 (1.3)	72 (27.5)	7 (9.7)	1 (4.8)
Quetiapine	2 (1.3)	2 (0.8)	0 (0.0)	1 (4.8)
Olanzapine	0 (0.0)	24 (9.2)	3 (4.2)	5 (23.8)
Zuclopenthixol	0 (0.0)	8 (3.1)	8 (11.1)	1 (4.8)
Donepezil	0 (0.0)	7 (2.6)	4 (5.6)	1 (4.8)
Flupentixol	0 (0.0)	5 (1.9)	1 (1.4)	2 (9.5)
Phenobarbital	0 (0.0)	2 (0.8)	2 (2.8)	0 (0.0)
Phenytoin	0 (0.0)	2 (0.8)	1 (1.4)	0 (0.0)
Valproic acid	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Duloxetine	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)

Multvariate analysis

Forward stepwise model building was done to identify a set of exemplary variables that best predict the outcome through a simple regression of each predictor variable verses the outcome. Akaike information criterion (AIC) was used as a statistical tool for parsimonious statistical model evaluation since it considers multiple models before selecting

the best model and can assess a complex model with multiple relationships simultaneously. A bivariate analysis of predictors with a p-value of less than 0.2, which was considered to be a more relaxed threshold was selected alongside those with the lowest Akaike information criterion (AIC) as the base for a multivariate model building. The variable that improved the model most was selected and a three variable regression carried out. The process was repeated until there was no further improvement in the model. The best predictor variables for the outcome were fluphenazine, haloperidol, amitriptyline and chlorpromazine as shown in tables 4, 5 and 6.

Table 4: Two variable model building

VARIABLE	AIC*
Fluphenazine	200.6945
Fluphenazine amitriptyline	192.5149
Flphenazine Benzhexol	202.4588
Fluphenazine chlorpromazine	197.0331
Fluphenazine fluoxetine	202.2067
Fluphenazine haloperidol	**185.8012**
Fluphenazine risperidone	202.0538

*Predictor with the lowest AIC value is in **bold**

Table 5: Three variable model building

VARIABLE	AIC*
Fluphenazine haloperidol	185.8012
Fluphenazine haloperidol amitriptyline	**173.5819**
Fluphenazine haloperidol benzhexol	187.7642
Fluphenazine haloperidol chlorpromazine	176.0813
Fluphenazine haloperidol risperidone	187.779

*Predictor with the lowest AIC value is in **bold**

Table 6: Four variable Model building

VARIABLE	AIC*
Fluphenazine haloperidol amitriptyline	173.5819
Fluphenazine haloperidol amitriptyline benzhexol	175.2613
Fluphenazine haloperidol amitriptyline chlorpromazine	**160.3943**

*Predictor with the lowest AIC value is in **bold**

DISCUSSION

This retrospective study analyzed potential drug-drug interactions in a population of hospitalized mentally ill patients at Mathari Mental Hospital between July and December 2013. The participants in study were nearly evenly distributed gender wise with a male preponderance and a mean age of 34.2 years. The average number of prescribed drug per patient was 6.5 this shows that poly pharmacy was high. The prevalence of potential serious drug-drug interaction at 30% was considered to be high, this was observed

mostly in participant with secondary level of education and married participants. Married participants had a statistically significant association with potentially serious drug-drug interaction (p=0.02) and unemployed participants having a statically significance of (p<0.01).

There is no scientific evidence to explain this association of married and unemployed with potential serious drug-drug interactions. However married and unemployed people may have stress due to the burdens associated with their social life. This explains the high number of these patients with mental illness captured in the study and significant association with potential drug interactions. However most social demographic characteristics in this study were not statistically associated with potentially serious drug-drug interactions. These findings concurs with a previous study where no associations were noted between demographic parameters including age, gender, marital or educational status and psychotropic drugs [27]. In this study demography appears to have a minimum impact on cross-sectional prescribing patterns in psychiatry patients so effort should be geared towards achieving rational, yet pragmatic treatment guidelines and logarithms to minimize risks while maximizing the benefits to these patients.

Ninety two percent of the participants did not have co-morbidities other than the diagnosed mental illness, hypertension accounted for 8% of the total patients. This seems not to concur with a similar study where the findings indicate that people with severe mental illnesses, such as depression or bipolar disorder have a higher cardiovascular mortality attributed to an increased risk of the modifiable coronary heart disease risk factors such as diabetes and hypertension [28]. In this study the low numbers of participants with diabetes and hypertension could be attributed to the fact that most of the sampled patients had a mean age of 34.2 years hence less prone to diabetes and hypertension conditions which are known to be prevalent in old age.

Most of the participants with potentially serious drug-drug interactions were diagnosed with bipolar mood disorder and schizophrenia. This explains the high use of haloperidol and fluphenazine, which had a statistically significant association with potentially serious drug-drug interactions. The use of fluphenazine as a monthly injection and haloperidol or chlorpromazine oral medication was common in this study. These drugs are known to prolong QTC interval of the heart which may lead to dizziness, syncope or cardiac arrest. The findings implies that patients on these drugs need close monitoring and periodic electro cardiogram (ECG) checkups [29, 30] which were a compulsory requirement among mentally ill patients who were on haloperidol and fluphenazine at Mathari Mental Hospital. There was no statistically significant association of potentially serious drug-drug interactions associated with the use of quetiapine or risperidone. This concurs with findings where the two drugs were found to have no association with prolongation of QTC interval [31]. To date, all antipsychotic drugs have the potential for serious adverse events. Balancing these risks with the positive effects of treatment poses a challenge for psychotherapy.

In this study, potentially serious pharmacokinetic drug interactions in patients on a combination of carbamazepine and diazepam were observed. Carbamazepine decreases the effect of diazepam by affecting CYP 3A4 metabolism. Significant pharmacokinetic metabolic interactions were observed in patients on carbamazepine and haloperidol. This could be attributed to the fact that these drugs are affected by cytochrome P450 (CYP) enzyme system. This findings concurs with a study where clinically significant pharmacokinetic drug interactions with antipsychotics and antidepressant drugs. The knowledge of substrates, inhibitors inducers of CYP isoenzyme may help clinicians to anticipate and avoid psychotherapeutic drug interactions and improve rational prescribing practices [32].

There was a significant additive pharmacodynamic drug interactions in first generation anti-depressant (amitriptyline) compared to second generation anti-depressant fluoxetine. This explains the results in a similar study where the potentially harmful pharmacodynamic drug interactions with first-generation anti-depressants had contributed to a gradual decline of their use in clinical practice. And second generation antidepressants have gradually replaced tricyclic antidepressants (TCAs) mainly because of their improved tolerability and safety profile [33].

A bivariate data analysis of drugs with serious drug interactions indicated that most of the drugs with a statistically significant association with the outcome

were substrates, inhibitors and inducers of cytochrome P450 isoenzyme with higher odds of developing a serious drug interaction in patients on fluphenazine. Forward step wise model building analysis indicated that the best predictor variables for serious drug interactions were fluphenazine, haloperidol, amitriptyline and chlorpromazine. According to WHO guidelines on pharmacological treatment of mental disorders in primary healthcare, the findings obtained in this study suggest necessity for continuous electrocardiogram monitoring which is mandatory in some countries for specific antipsychotics for example haloperidol. Further monitoring of full blood count, urea and electrolytes and liver function tests, blood glucose levels is crucial in an effort to balance the risks and benefits of the drugs before using them [34].

CONCLUSION

The obtained results show that the prevalence of potentially serious drug interactions was high among admitted patients at Mathari Mental Hospital. Married and unemployed patients were more likely to have potentially serious drug interactions. Patients on fluphenazine, haloperidol, amitriptyline and chlorpromazine are at a higher risk of having potential serious drug-drug interactions. These drugs exhibited both pharmacodynamic and pharmacokinetic interaction mechanisms.

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Conflict of Interest Reported: Nil; Source of Funding: None Reported