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Original Research Article

Appraisal and discernment of prevalent drug-drug interactions in patients with psychiatric disorders

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ABSTRACT

Background: Drug-drug interactions **(**DDIs) contribute majorly to hospital admissions, treatment failures, avoidable medical complications and subsequent healthcare costs. Thus, we employ a mechanistic approach to prospectively investigate the incidence of potential DDIs in the psychiatric patients in a clinical setting.
Methods: In this prospective, observational, multi centred study conducted for a span of 6 months, psychiatric inpatients (≥18 years) prescribed with 2 or more medications daily for any medical illness were included. The secured prescriptions of the inpatients selected in accordance to the inclusion criteria were then assessed for DDIs using Micromedex$^{(TM)}$ as a standard.
Results: Of the total 400 enrolled participants, 383 (95%) of them showed at least one pDDI regardless of the severity. An average of 7.33 interactions per patient was also deduced. A high prevalence of pDDIs totalling to 2900 was recorded in our study with an average of 7.33 interactions per patient. Most of the interactions were of major (56.52%) and moderate severity (39.07) followed by contraindicated (2.55) and minor (1.83). Cardiovascular system (41.77%) had the highest potential to be affected due to the pDDIs identified. Trihexyphenidyl, haloperidol, promethazine, amisulpride, risperidone, divalproex, trifluoperazine, olanzapine and clozapine where among the most commonly encountered drugs in these interactions.
Conclusions: A high prevalence of pDDIs totalling to 2900 was recorded in our study with an average of 7.33 interactions per patient. A significant association of the pDDIs with variables such as age, gender, diagnosis and total number of drugs used was identified. More studies are required to explore the overall pattern of DDIs in psychiatric patients along with their levels and correlation with different risk factors. Careful monitoring and documentation are necessary to prevent further complications thereby improving the therapeutic outcome.

Keywords: Prevalence, DDIs, Psychotropic drugs

INTRODUCTION

Psychiatric disorder

The diagnostic and statistical manual of mental disorders, 5th edition (DSM-V) promulgated the definition of psychiatric disorder as a behavioural or psychological syndrome or pattern that causes significant distress or impairment of personal functioning in an individual.[1] The features presented by a mental illness may be persistent, worsening and remitting, or occur as a single episode. Many disorders have been described, with signs and symptoms that vary widely between specific disorders. The causes of mental disorders are often unclear. Mental disorders are generally characterized by some combination of abnormal thoughts, emotions, behaviour and relationship with others.[2] Absence of mental health is a great burden to the economic, political and social functioning of human beings, society, and nation. The major psychiatric disorders as per DSM-V, a standard language to communicate about diagnostic criteria and classification of mental disorders, are neurodevelopmental

disorders, schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, depressive disorders, anxiety disorders, obsessive-compulsive and related disorders, trauma- and stressor-related disorders, dissociative disorders, somatic symptom and related disorders, feeding and eating disorders, elimination disorders, sleep-wake disorders, sexual dysfunctions, gender dysphoria, disruptive/impulse-control/conduct disorders, substance-related and addictive disorders, neurocognitive disorders, personality disorders, paraphilic disorders, and other mental disorders.[3]

Prevalence of psychiatric disorders

Indian scenario

India has a lifetime mental morbidity of 13.9% with a suicidal risk of 6.4%.[4] The prevalence of mental illness in India is 58.2 and 73 per 1000 population as reported by meta-analysis of certain epidemiological studies.[5] One of the costliest mental illness in terms of both human suffering and social expenditure is schizophrenia.[6] About 5-10 in 1000 people are affected with schizophrenia in India.[7] In India, there is no nationwide study to evaluate the prevalence rates of BPAD.[8] 0.5% Indians suffer from this disorder.[2,7]

Global scenario

According to Felker et al, psychiatric patients have more than twice the standardized mortality ratios for both natural and unnatural causes of death when compared to that of the general population.[9] Schizophrenia is estimated to have a lifetime prevalence of 0.3-0.7% worldwide.[6] A recent international review[10] of both DSM-IV bipolar I and II disorders in population studies yielded an aggregate cross-study lifetime prevalence estimate of 1.2%, ranging from 0.1% in Nigeria[11] to 3.3% in the U.S..[12] Another common mental disorder is depression and is one of the main causes of disability universally. Globally, an estimated 300 million people are affected by depression.[2] Worldwide, 47.5 million people have dementia.[2]

Psychotropic treatment[13]

At present, mental disorders are managed by psychological or biological treatment. Approaches in psychological therapies include cognitive therapy, behavioural therapy, family focused therapy or psychoanalysis. Biological therapy for mental disorders generally involves the use of some form of physical intervention (such as pharmacotherapy). The medicines with specific abilities to produce effects upon emotion and behaviour and which are most commonly used in the management of mental disorders are often referred to as psychotropic drugs. This area of pharmacology is also known as psychopharmacology.

Drug-drug interactions (DDIs)

A DDIs 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.[14] DDIs can lead to alteration of therapeutic response or increase untoward effects of many drugs.[15] Old age, taking increased number of medications, long hospital stays, gender and co morbid conditions have been reported as common risk factors for DDIs.[16] As most psychotropic medications are metabolized by the cytochrome (CYP) enzyme system, it may be predicted that the risk of DDIs will increase as a result of polypharmacy.[17] The issue of DDIs 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.[15] Drug interactions between the drugs vary with changes in their underlying mechanism. Drug interactions are categorized into behavioural, pharmaceutical, pharmacokinetic, and pharmacodynamic DDIs.[18]

DDIs in psychiatry

The breakthrough of new psychopharmacologic agents facilitated the availability of more therapeutic options but has also complicated the patient treatment. The likelihood of drug interactions in psychiatry is attributed to combination therapy which culminates as an increased risk of adverse outcomes to the patients.[19] There exists a variation in the significance of a drug interaction between individuals depending on factors like co-morbidities, gender, and age.[20] Psychiatric medications can account for up to 50% of the ADRs in hospitalized psychiatric patients, multiple of which can be attributed to DDIs as revealed by a recently published study.[21] Guo et al have reviewed the medical records of health insurance system and detected potentially dangerous drug interactions in approximately 23% of patients taking antipsychotic medications.[22] Another study revealed that DDIs account for an estimated 26% of ADRs requiring hospital admissions whereas prevalence of DDIs in psychiatric hospital settings has been estimated in some studies to be in the range of 27.8 to 51.4 %.[23,24] Hence it is important to contemplate potentially hazardous interactions in psychiatry.

Prevalence of psychiatric DDIs

Global and Indian scenario

An elevation in the elderly population world-wide has led to concerns regarding the burden of DDI-related ADRs. Attributing to the specific characteristics of the elderly such as physiologic modifications related to ageing processes, the prevalence of pDDIs is elevated in the elderly and ranges from 42.5 to 54.4%.[25] In a prospective study conducted in Taiwan, a total of 130 potential interactions were detected in 339 (63.1%) of the 537 medication profiles.[26] Lima and De Bortoli Casiani

demonstrated that incidence of DDIs increases by 10-20% in patients using 10-20 drugs.[27]

A recent study from India on the incidence and predictors of adverse drug reactions caused by DDIs in psychiatric patients was found to be 12%. Pharmacodynamic interactions accounted for the majority (68.5%) of ADRs. The greatest propensity to interact with other medications was exhibited by risperidone with 41 occurrences.[28]

In this study, the authors aimed to assess commonly occurring pDDIs, the psychiatric diagnosis of patients in the study, manifestation of comorbidities, customary psychotropic use, prevalence of pDDIs and their classification based on severity/documentation/onset, adverse clinical outcomes of pDDIs, and common interacting drug combinations with their probable mechanism of interaction along with their clinical management. This observational study also determines the statistical association of parameters like age, gender, comorbidity, diagnosis, body system, onset, documentation, psychotropic and non-psychotropic drug use against different severities of pDDIs.

METHODS

This prospective, observational, multi centered study was of 6 months duration conducted from October 2017 to March 2018 on patients under inclusion criteria. The four study sites were: site I -Bharati hospital and research center, Dhankawadi, Pune-411043; site II-Chaitanya institute for mental health, Bhagat Puram, Khadi Machine Chowk, Pune- 411048; site III-Chaitanya Institute for Mental Health, Behind Wonder City, Katraj, Pune-411046; site IV-Chaitanya institute for mental health, popular prestige commercial complex, Warje, Pune-411052. Psychiatric inpatients (≥18 years) prescribed with 2 or more medications daily for any medical illness were included in the study. The exclusion criteria were medico-legal cases of any kind and interactions of herbal/topical medications.

We determined the recommended sample size using Raosoft sample size calculator.[31] Considering parameters like margin of error, confidence level, population size, response distribution as 5%, 95%, 20000, 50% respectively, our recommended sample size was 377. However, we proceeded with 400 as our final sample size.

Micromedex (TM), an online evidence-based database was used for identifying DDIs in the study. It includes "in-line" referenced information about drugs, toxicology, diseases, acute care, and alternative medicine for healthcare professionals to make informed clinical diagnosis and treatment decisions. It is a source of quick and reliable drug information.

Ethical approval for the study was obtained from the ethics committee of Bharati medical college and Chaitanya institute for mental health. Inpatients were selected in accordance to the inclusion criteria. Detailed information regarding the study objectives were explained to the patients and consent was taken thereby ascertaining their willingness to participate in the said study. Prescriptions were procured for demographic details (e.g., patient' s name, age, sex, date of admission), confirmed diagnosis, current medication (with brand and generic name, date started and stopped). The required details were noted in the self-predesigned patient profile form. The prescriptions were assessed for DDIs using Micromedex(TM) as a standard. During assessment of drug interactions, the DDIs were assembled depending on the parameters defined by Micromedex (TM). The classifications made to assess drug interactions and to formulate the results were according to severity (Contraindicated/major/moderate/minor/ unknown), effect on body system (Cardiovascular/ neurologic/ANS/hematologic/endocrine and metabolic/ respiratory/others), onset (Not specified/ Rapid/Delayed), documentation (Excellent/ good/fair/unknown), probable mechanism (QT prolongation/CNS depression/delayed gastric emptying, etc.), and clinical management (Monitor ECG/separate administration of two interacting drugs by at least 2 hours/monitor glucose levels/monitor for signs of toxicity, etc.).

The severity of drug interactions as defined by Micromedex(™) were contraindicated (the drugs are contraindicated for concurrent use), major (the interaction may be life threatening and/or require medical interventions to minimise or prevent serious adverse effects), moderate (the interaction may result in exacerbation of the patient's condition and/or require alternate therapy), minor (the interaction would have limited clinical effects. Manifestations may include an increase in the frequency or severity of the side effects but generally would not require a Major alteration in therapy), and unknown (Unknown).[32]

The chi-square test was used to establish the association between the categorical variables. P values were obtained from the Chi square calculator.[37] The associations were established against contraindicated drug interactions (Dis), major DIs, moderate DIs, minor DIs, unknown DIs and total number of DIs. Parameters which were considered for association are age, gender, presence and absence of comorbidity, psychiatric diagnosis, clinical outcome of DIs i.e., the body system affected, onset of DIs, documentation of DIs, psychotropic, and non-psychotropic drugs administered to patient.

RESULTS

General patient characteristics

For the sample size of 400, the margin of error was found to be 4.85% according to Raosoft sample size calculator considering parameters like confidence level, population size, response distribution as 95%, 20000, 50% respectively. This study consisting of a total number of 400 patients, had 252 (63%) male and 148 (37%) female [male

to female ratio being 252:148] participants with a mean age of 46.24±16.81 years. Around 161 patients diagnosed with psychiatric disease belong to the age range of 31 to 50 years accounting up to 40.25% of the patients under study (Table 1).

Table 1: Demographic profile of the study participants.

Demographic profile	Frequency	Percent (%)
Age range (years)		
10 to 20	18	4.5
21-30	68	17
31-40	76	19
41-50	85	21.25
51-60	65	16.25
61-70	50	12.5
71-80	28	7
81-90	8	2
91-100	2	0.5
Sex		
Male	252	63
Female	148	37

In the total 3375 drugs prescribed, 2053 (60.83%) were psychotropic whereas 1322 (39.17%) were given for underlying co morbid conditions. An average of 8.44 medications per patient was also identified. The number of orally administered drugs were 3117 (92.36%), 222 (6.58%) administered intramuscularly, 33 (0.68%) intravenously and 3 (0.09%) subcutaneously. Amongst the registered patients, the most prevalent diagnosis was found to be schizophrenia with a total of 225 patients followed by mental retardation with psychosis (38) and bipolar disorder (31) (Table 2). This study also analysed patients suffering from various co-morbid conditions for which they were being prescribed medications along with antipsychotics. Such patients came to a total count of 284 (71%) (Figure 1). The study provides information regarding the most commonly used psychotropics by patients from all the 4 four sites. The highly used antipsychotic was discovered to be trihexyphenidyl (9.8%) with the least being quetiapine (2.22%) (Figure 2).

Table 2: Psychiatric diagnosis of patients in the study.

Psychiatric diagnosis	Frequency	Percent (%)
Schizophrenia	225	56.25
Bipolar disorder	31	7.75
Alcoholic dependence syndrome	30	7.5
Dementia	17	4.25
MR + psychosis	38	9.5
Depression	12	3
Substance Induced	20	5
Others	27	6.75

MR: Mental Retardation, Others: Serotonin Syndrome (8); Increased exposure to CYP2D6 substrate (5); Potential toxicity like sedation (2), confusion (3), cardiac arrhythmias (1), orthostatic hypotension (1), hyperthermia (5), extrapyramidal effects (2).

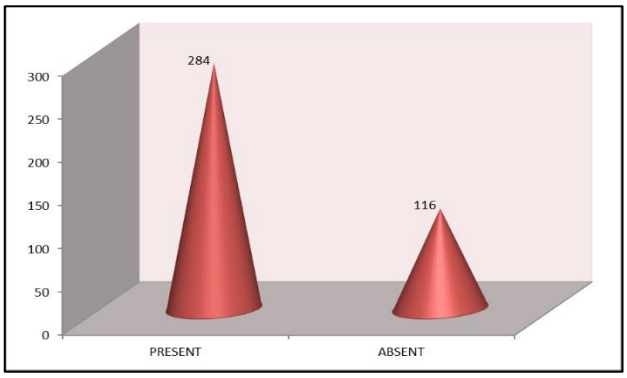

Figure 1: Manifestation of comorbidities in the patients under study.

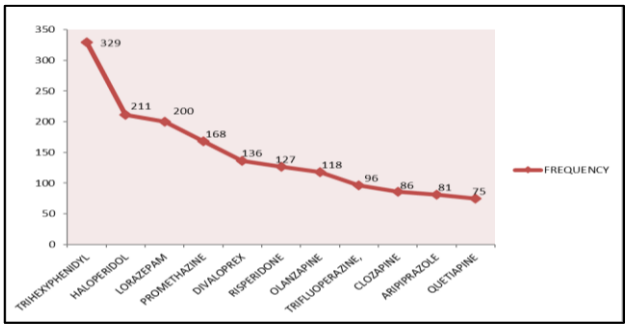

Figure 2: Customary psychotropic use in the enrolled patients.

Prevalence of pDDIs

Of the total 400 enrolled participants, 383 (95%) of them showed at least one pDDI regardless of the severity. An average of 7.33 interactions per patient was also deduced.

Levels of pDDIs

Based on the onset, severity and scientific evidence, the identified pDDIs were catalogued into different levels. Amidst the total 2900 pDDIs determined, most belonged to the major (1639) and moderate (1133) severities followed by contraindicated (74) and minor (53) severities. The highest number of pDDIs was found to be in the major severity (56.52%) of a majority had a fair documentation with onsets not specified. Appraisal of the scientific evidence revealed a total of 137 pDDIs with an excellent documentation, 750 with good and a maximum of 2013 with fair documentation. Similarly, on assessing the onset of the pDDIs, (219) were with rapid onset, (862) delayed onset and (1819) were with non-specified onset (Table 3).

Effect of pDDIs on the body system

Upon evaluation, it was found that the cardiovascular system (41.77%) had the highest potential to be affected

due to the pDDIs identified. A systematic review of the said parameters is reflected in Table 4.

Common interacting drug combinations

The common interacting drug combinations of each severity along with their frequencies are given in Table 5. Trihexyphenidyl, haloperidol, promethazine, amisulpride, risperidone, divalproex, trifluoperazine, olanzapine, and clozapine where among the most commonly encountered drugs in these interactions.

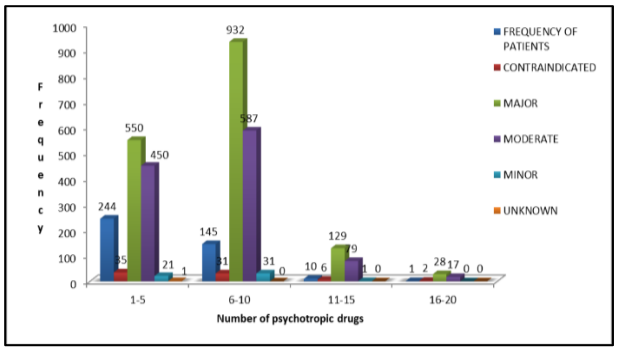

Figure 3: DIs seen with the use of psychotropic medicines by patients diagnosed with psychiatric disorders.

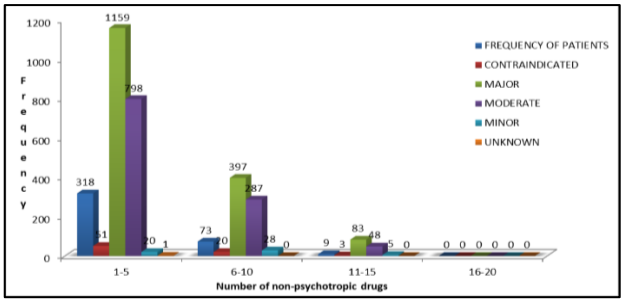

Figure 4: DIs seen with the use of non-psychotropic medicines by patients diagnosed with psychiatric disorders.

Statistical significance of the result

According to the chi-square test used, association between categorical variables were established against contraindicated, major, moderate, minor, unknown, and total number of DIs.[37] Parameters which were considered for association are shown in the table below and those with strong significant associations are highlighted (Table 6.). The results were found to be significant at $p<0.05$.

Table 3: Classification of identified pDDIs.

Level	Frequency, (n=400)	Percent out of total DIS (%)
Severity		
Contraindicated	74	2.55
Major	1639	56.52
Moderate	1133	39.07
Minor	53	1.83
Unknown	1	0.03
Documentation		
Excellent	137	4.72
Contraindicated	0	0
Major	47	1.62
Moderate	86	2.96
Minor	4	0.13
Unknown	0	0
Good	750	25.86
Contraindicated	4	0.13
Major	191	6.58
Moderate	538	18.55
Minor	16	0.55
Unknown	1	0.03
Fair	2013	69.41
Contraindicated	70	2.41
Major	1401	48.31
Moderate	509	17.55
Minor	33	1.13
Unknown	0	0
Onset		
Rapid	219	7.55
Contraindicated	4	0.13
Major	35	1.20
Moderate	152	5.24

Continued.

Level	Frequency, (n=400)	Percent out of total DIS (%)
Minor	27	0.93
Unknown	1	0.03
Delayed	862	29.72
Contraindicated	0	0
Major	97	3.34
Moderate	745	25.68
Minor	20	0.68
Unknown	0	0
Not specified	1819	62.72
Contraindicated	70	2.41
Major	1507	51.96
Moderate	236	8.13
Minor	6	0.20
Unknown	0	0

Table 4: Adverse clinical outcomes of pDDIs in the enrolled patients.

Body system effect	Frequency (n=3184)	Percentage (%)
Cardiovascular	1330	41.77
Contraindicated	72	2.26
Major	1209	37.97
Moderate	46	1.44
Minor	3	0.09
Unknown	0	0
Decreased plasma concentration	497	15.61
Contraindicated	0	0
Major	26	0.81
Moderate	449	14.10
Minor	22	0.69
Unknown	0	0
Increased plasma concentration	326	10.23
Contraindicated	0	0
Major	66	2.07
Moderate	254	7.97
Minor	6	0.188
Unknown	0	0
Autonomic nervous system	319	10.01
Contraindicated	0	0
Major	73	2.29
Moderate	246	7.72
Minor	0	0
Unknown	0	0
Neurological	280	8.79
Contraindicated	1	0.031
Major	166	5.21
Moderate	91	2.85
Minor	21	0.659
Unknown	1	0.031
Hematologic	167	5.24
Contraindicated	0	0
Major	114	3.58
Moderate	51	1.60
Minor	2	0.062
Unknown	0	0
Endocrine	70	2.19
Contraindicated	0	0
Major	29	0.91
Moderate	41	1.028

Continued.

Body system effect	Frequency (n=3184)	Percentage (%)
Minor	0	0
Unknown	0	0
Musculoskeletal	10	0.31
Contraindicated	0	0
Major	7	0.21
Moderate	2	0.062
Minor	1	0.031
Unknown	0	0
Metabolic	48	1.50
Contraindicated	0	0
Major	25	0.78
Moderate	23	0.72
Minor	0	0
Unknown	0	0
Respiratory	36	1.13
Contraindicated	0	0
Major	35	1.09
Moderate	1	0.031
Minor	0	0
Unknown	0	0
Gastrointestinal	1	0.031
Contraindicated	1	0.031
Major	0	0
Moderate	0	0
Minor	0	0
Unknown	0	0
Other	100	3.14
Contraindicated	2	0.062
Major	52	1.63
Moderate	46	1.44
Minor	0	0
Unknown	0	0

Table 5: Top 5 interacting drug combinations of each severity.

Variables	N	Effect on body system	Onset	Documentation	Probable mechanism	Clinical management
Contraindicated, (n=74)						
Amisulpride x Clozapine	15 (20.27)	Cardiovascular	Not Specified	Fair	Additive QT prolongation	Contraindicated
Amisulpride x Promethazine	9 (12.16)	Cardiovascular	Not Specified	Fair	Additive QT prolongation	Contraindicated
Amisulpride x Quetiapine	6 (8.11)	Cardiovascular	Not Specified	Fair	Additive QT prolongation	Contraindicated
Amisulpride x Olanzapine	6 (8.11)	Cardiovascular	Not Specified	Fair	Additive QT prolongation	Contraindicated
Amisulpride x Apipiprazole	6 (8.11)	Cardiovascular	Not Specified	Fair	Additive QT prolongation	Contraindicated
Major, (n=1639)						
Haloperidol x Promethazine	82 (5.00)	Cardiovascular	Not Specified	Fair	Additive effects on QT interval	Monitor ECG
Haloperidol x Risperidone	45 (2.75)	Cardiovascular	Not Specified	Fair	Additive QT interval prolongation	Avoid concomitant use
Haloperidol x Trifluoperazine	40 (2.44)	Cardiovascular	Not Specified	Fair	Additive QT prolongation	Avoid concomitant use
Lorazepam x Olanzapine	38 (2.32)	Cardiovascular/ Respiratory	Not Specified	Fair	Additive CNS depression	Avoid concomitant use

Continued.

Variables	N	Effect on body system	Onset	Documentation	Probable mechanism	Clinical management
Pomethazine x Haloperidol	38 (2.32)	Cardiovascular	Not Specified	Fair	Additive effects on QT interval	Monitor ECG
Moderate, (n=1133)						
Trihexyphenidyl X Haloperidol	117 (10.33)	ANS	Delayed	Good	Additive anti-cholinergic effects	Dosage adjustments required
Trihexyphenidyl X Promethazine	103 (9.09)	ANS	Delayed	Fair	Delayed gastric emptying	Anticholinergic use to be re-evaluated every 3 months
Trihexyphenidyl x Divalproex	99 (8.74)	Decreased Plasma Concentration	Delayed	Fair	Unknown	Dose adjustment for valproate sodium
Trihexyphenidyl x Trifluoperazine	97 (8.56)	ANS	Delayed	Fair	Delayed gastric emptying	Anticholinergic use to be re-evaluated every 3 months
Divaloprex x Lorazepam	67 (5.91)	Increased Serum Concentrations	Rapid	Good	Decreased lorazepam metabolism	Monitoring required
Minor, (n=53)						
Clozapine x Lorazepam	19 (35.85)	Neurologic	Rapid	Fair	Additive	Reduce or eliminate caffeine exposure
Calcium Chloride x Ferrous Fumarate	4 (7.55)	Decreased Plasma Concentration	Delayed	Fair	Decreased iron absorption	Iron salts should be taken 1 hr before/after calcium
Aspirin x Ranitidine	4 (7.55)	Increased/ decreased plasma concentration	Not Specified	Excellent	Reduced absorption of iron	Coadministration with caution
Lorazepam x Caffeine	4 (7.55)	Decreased Plasma Concentration	Rapid	Good	CNS antagonistic effects	Reduce/eliminate caffeine exposure
Ascorbic acid x Cyanocobalamin	2 (3.77)	Decreased Plasma Concentration	Delayed	Good	Unknown	Separate Administration by at-least 2 h
Unknown, (n=1)						
Lorazepam x Caffeine	1 (100)	Neurologic	Rapid	Good	CNS-anta-gonistic effect	Reduce caffeine exposure

Table 6: Association of parameters of different pDDIs.

Parameters	Contra indicated	Major	Moderate	Minor	Unknown	Total no. of DIs	Total no. of drugs
Age (Years)	0.01942	0.4625	0.5166	0.4588	0.7763	0.8403	-
Gender	0.001444	0.001676	0.060666	0.006035	0.1929	0.002854	0.140013
Comorbidity	0.40827	0.00685	0.00004	0.006403	0.1188	0.000562	0.00133
Diagnosis	0.009494	0.000005414	0.001006	0.2944	0.116	0.00006919	0.00152
Body system	0	0	0	0	0.5003	1	-
++++Onset	<0.00001	<0.00001	<0.00001	<0.00001	0.002253	1	-
Documentation	0.00001722	<0.00001	<0.00001	<0.00001	0.2389	0.877	-
Psychotropic	0.002546	0	0	0.02017	0.8876	0	0.00001109
Non-psychotropic	0.1254	0.0008917	0.001671	0	0.8791	0.0002478	0.000003155

DISCUSSION

Based on our estimation, a comprehensive assessment of the identification of DDIs selectively in psychiatric pharmacotherapy is very rare in Indian settings. Our study strived to bridge this deficit by employing a mechanistic approach by prospectively investigating the incidence of potential DDIs in the psychiatric patients in a clinical setting.

In Pakistan, Ismail et al had conducted a similar study enrolling a total of 415 patients.[24] Mezgebe et al, who carried out the study in Ethiopia, however just had 216 participants.[33] Our study consisted a total of 400 patients. Age wise, we saw a median of 45 years which was different from others (25-27 years). Based on the male female ratio, both the above-mentioned studies almost had an equal proportion (male (47-54%): female (47-53%).[24,33] However in our study, we had a greater percentage of males enrolled (63:37%). Diagnosis wise, Mezgebe et al had reported that patients with schizophrenia was seen the most (57%).[33] Coincidently, the same case was also seen in our study (56.25%).

Like us, most of the studies involved with a similar objective used Micromedex as their standard.[24,28,34,38]. Sengul et al though, used Drugs.com as their standard for reference.[35] While considering the total number of pDDIs seen per study, as of yet Mezgebe et al had reported a greater number with 81.8% of their patients suffering from at least one pDDI regardless of the severity.[33] In comparison, Ismail et al and Lucca et al had reported a relatively lower percentage (64.8%; 55.2%).[24,28] During the duration of our study however, we had discovered an exorbitant amount of pDDIs accounting up to 95%.

Assessment of severity is essential to qualify the medical risk of the interaction.[36] All the studies showed a lower proportion of pDDIs with "contraindicated" severity (0.5-3%).[24,28,33] Our study also had the same inclination. Based on the "major" severity, the mentioned studies showed results in the range of 15-43%.[24,28,33-35] In contrast, we determined a higher level of the said severity (56.52%). Furthermore, we also saw a lower level of those with "moderate" severity (39.07%) than the others (50-87%).[24,33-35] Only Lucca et al had identified a similar level as us. When analyzing the "minor" severity, we saw that Lucca et al showed a rate of 34.82%.[28] This was higher than what was seen with the others (0.2%-5%).[24,33-35] Nevertheless, the amount of "minor" pDDIs in our dissertation fell in the range that was seen in majority of the studies (1.83%). Most of the studies produced the maximum number of pDDIs in "moderate" severity (50-90%).[24,28,33-35] Whereas, ours produced the highest number with "major" severity (56.52%); others being of the range 15-43%.[24,28,33-35]

Onset of action of the pDDIs is another essential parameter as it indicates how quickly the interaction may occur.[36] In previous studies, the reported pDDIs with "rapid" onset generally fell in the range of 3-24%.[24,28,33,34] Similarly, so did our study (7. 55%). However, our study also reported a decreased level pDDIs with "delayed" onset (29.72%) than others (50- 81%).[24,28,33,34] This is mainly because we had a higher level of pDDIs with "not specified" documentation than them (62.72%).[33,34]

Documentation of a pDDI detects the quality and quantity of the medical literature supporting the inclusion in the data.[36] Ismail et al reported 4.6% of their pDDIs with excellent documentation.[24] Even we recorded a similar level (4.72%). Their percentage of pDDIs with "good" documentation was higher than those with "fair" documentation (66.4%> 29%).[24,33] Our study though, produced the opposite result [fair (69.41%) > good (25.86%)].

The comparison of the clinical outcomes determined in our dissertation was done in relation to Sengul et al.[35] The study detailed a higher risk of ANS related clinical outcomes (38.6%) of all drug interactions. In contrast, we recorded a lower level at 9.84%. They even detailed an elevated level of interaction affecting the respiratory (24.5%) and hematological system (11.9%) than us (1.11%: 5.15%). However, our study reported a higher number of interactions affecting the cardiovascular system (41.01%) than them (14.6%).[35]

We discovered that the highest number of pDDIs occurred in the age group between 40-51 years totalling up to 676. However, these findings were inconsistent with the results of certain studies.[24] A study conducted by Guo et al reported a statistically significant association with gender, diagnosis, co morbidities and race.[22] Similarly, our findings showed a statistically significant association with variables such as age, gender, diagnosis, comorbidities and the total number of drugs administered. As ours was a study focusing on patients of the Indian origin, race wasn't a significant factor.

There were potential limitations in this study. The actual effects of the identified pDDIs were not evaluated. Further studies are needed to identify actual clinical consequences of these interactions. The enrolled patients were not continuously evaluated during their entire hospital stay. Irregular follow-up might lead to inconsistency in result. Micromedex(TM) was used for screening of pDDIs in this study while multiple screening resources were used by other researchers. The study was generalized as it was conducted in a tertiary care hospital. Hence, only the pDDIs of the specific drug prescription pattern is determined. Interactions of herbal and topical medications were not evaluated in the study.

Future direction

Future studies should consider the use of larger sample size. Assessment of ADR's due to DDI's in patients can also be evaluated. Standard treatment guidelines should be made considering most prevalent DDI's, which will reduce

incidence of ADR's in psychiatric patients. As the number of uses of psychotropic medications is on a rise, the pharmacist's role too needs to be extensive. The pharmacists can serve as an excellent source to assist physicians in their prescribing and counselling patients about psychotropic medications. Documentation of DDI's in specific population is of great importance, which needs a strong nationwide DDI reporting structure.

CONCLUSION

A high prevalence of pDDIs totalling to 2900 was recorded in our study with an average of 7.33 interactions per patient. Most of the interactions were of major (56.52%) and moderate severity (39.07) followed by contraindicated (2.55) and minor (1.83). A significant association of the pDDIs with variables such as age, gender, diagnosis and total number of drugs used was also identified. A majority of the population affected by the identified pDDIs belonged to the adult age group (41-50) and of the male gender. Schizophrenia was found to be the common diagnosis among the enrolled patients (225). Upon theoretical analysis a high number of the clinical outcomes were found to have an effect on the cardiovascular system (41.01%). Trihexyphenidyl, haloperidol, lorazepam, promethazine, divalproex, olanzapine and risperidone were the commonly used antipsychotics and trihexyphenidyl with haloperidol (10.33%), trihexyphenidyl with promethazine trihexyphenidyl (9.09%) with divalproex (8.74%), trihexyphenidyl with divalproex (8.56%) were the most prevalent interactions seen in our study. More studies are required to explore the overall pattern of DDIs in psychiatric patients along with their levels and correlation with different risk factors. Careful monitoring and documentation are necessary to prevent further complication thereby improving the therapeutic outcome.

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