Prevalence of Potential Drug-drug Interactions among Psychiatric Patients at Psychiatry Hospital in Sulaimani City

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Abstract:

Background: Clinically significant drug-drug interactions can be defined as events in which the pharmacodynamics or pharmacokinetic characteristics of a drug are modified by coadministration of a second drug to the patient's medication protocol, which can often lead to in an increase of serious adverse reactions. The probability of interactions increases with higher number of drugs administered.

Objective: The objective of this prospective study was to determine the prevalence of potential psychotropic drug-drug interactions among hospitalized patients at Psychiatry hospital in Sulaimani city, and to identify the clinical consequence of such combinations.

Method: The current study was involved recruiting the data regarding prescribed psychotropic drugs of 60 newly hospitalized psychiatric patients. Data collection on each individual patient was performed on the specific patient dossier of to report any potential psychotropic drug-drug interactions utilizing Medscape drug interaction checker for identification of the different types of drug-drug interactions.

Result: The prevalence of potential drug-drug interaction at Psychiatry Unit in Sulaimani city in 60 patients was 98%, of which 16.6% were major drug-drug interactions. The most frequently prescribed medications were antidepressant drugs, most of patients received more than four drugs.

Conclusion: From the current study one can conclude that there was a high prevalence of potential drug-drug interactions among psychiatric patients, which was more frequent in patients taking more than one psychotropic medication.

Key words: Drug-drug interactions, psychotropics.

مدى انتشار التفاعلات الدوائية المحتملة بين المرضى النفسيين في مستشفى الطب النفسي في مدينة السليمانية

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الخلاصة:

الخلفية: يتم تعريف التفاعلات الدوائية الدوائية ذات الأهمية السريرية على أنها الأحداث التي يتم فيها تغير الديناميكيات الدوائية أو الخصائص الحركية الدوائية عن طريق إضافة دواء ثان إلى نظام الدواء الخاص بالمريض، والذي يمكن أن يؤدي غالبا إلى زيادة التفاعلات الجانبية الخطيرة. يزداد إحتمال التفاعلات مع زيادة عدد الأدوية المعطاة في ان واحد.

الهدف: كان الهدف من هذه الدراسة المستقبلية هو تحديد مدى انتشار التداخلات الدوائية الدوائية ذات المؤثرات العقلية المحتملة بين المرضى فى مستشفى الطب النفسى في مدينة السليمانية، وتحديد النتائج السريرية لمثل هذه التداخلات.

الطريقة: تضمنت الدراسة جمع البيانات المتعلقة بالمؤثرات العقلية الموصوفة لـ 60 مريضا نفسيا دخلوا المستشفى حديثا من كلا الجنسين. وقد تم إجراء جمع البيانات عن كل مريض على حدة في ملف المريض المحدد للإبلاغ عن أى تداخلات دوائية ذات مؤثرات عقلية محتملة باستخدام مدقق التفاعلات الدوائية Medscape لتحديد الأنواع المختلفة للتداخلات الدوائية الدوائية.

النتيجة: بلغ معدل انتشار التفاعلات الدوائية المحتملة في وحدة الطب النفسي في مدينة السليمانية لدى 60 مريضا 98%، منها 35% تفاعلات دوائية رئيسية. وكانت الأدوية الأكثر وصفا هي الأدوية المضادة للإكتئاب. تم وصف أكثر من 4 أدوية لمعظم المرضى.

الإستنتاج: خلصت الدراسة إلى إرتفاع معدل إنتشار التداخلات الدوائية المحتملة بين المرضى النفسيين، وهو أكثر شيوعا في المرضى الذين يتناولون أكثر من دواء ذات تأثير عقلى.

الكلمات المفتاحية: التفاعلات الدوائية، المؤثرات العقلية.

Introduction:

A drug-drug interaction is known as a clinically significant alteration in the effect of a drug as a result of coadministration of another drug and is either pharmacodynamic or pharmacokinetic type of interaction leading to various effects (1). Drug-drug interactions can cause adverse drug reactions that must be prevented (2). Potential drug-drug interactions should be differentiated from verified interactions seen in patients. Reports focusing on drug-drug interactions in psychiatric patients are mainly targeting specific drug classes or adverse reactions. Moreover, several authors have revealed individual criteria to find potential drug-drug interactions in psychiatric patients that involve a coadministration of cytochrome inducers or inhibitors and their affecting drugs, concomitant administration of more than one anticholinergic drug, and drugs that possibly cause prolongation of the QT interval (3).

Despite that the monotherapy is the standard regimen recommended in numerous treatment guidelines of antipsychotics. However, because of the sparse efficacy of monotherapy, antipsychotic polypharmacy is frequently used (2,3). In spite of the insufficient proof of its efficacy and safety, polypharmacy involving antipsychotic drug combinations is common. The issue of acquired QT prolongation and torsades de pointes (TdP) is more worsened in patients prescribed polytherapy (4). Previous reports have found that the prevalence of drug-drug interactions in patients prescribed five drugs concomitantly is approximately 40%, this percentage significantly increases and surpasses 80% in patients being given seven or more drugs (5).

It is known that drug-drug interactions are considered as the most frequent causes of increased hospitalizations, morbidity, and mortality. It is conceivably a significant aspect for the incidence of adverse drug reactions. Studies have revealed that 5% of the adverse drug reactions that occur in hospitals are because of drug-drug interactions (6). Potential drug-drug interactions could be anticipated from the pharmacological activities of the drugs and possess the probability to change the

actions of the concomitantly prescribed drug.

On the other hand, all potential drug-drug interactions may not favor clinically crucial interactions by definition. However, potential drug-drug interactions may require closer monitoring. Several Pharmacoepidemiological studies conducted worldwide with different study settings and design have reported the prevalence rates of potential drug-drug interactions, varying from 5% to 91% (7). Patients with psychiatric diseases are at risk for drug-drug interactions since they are expected to use chronic therapy of multiple medications to reduce and control the signs and symptoms of their diseases (8,9).

The concomitant use of five or more various medications is known as polypharmacy. It has a high prevalence in both outpatient and inpatient situations, specifically in elderly patients (10). Most pharmacokinetic drug interactions in psychiatry are linked to the cytochrome P450 associated drug metabolism, although the outcomes of enzyme induction are difficult to anticipate (11). While pharmacodynamic drug interactions occur when the pharmacological action of a drug is affected by another drug. An example of this type of interaction is when anticholinergic drugs or drugs with QT interval prolonging properties are combined. Anticholinergic drugs inhibit the effects of acetylcholine on central and peripheral acetylcholine receptors and may result in diffuse adverse drug reactions (12).

There is no doubt regarding beneficial effects of medications, but they are still accompanied by probability of drug interactions, adverse effects and other drug-related problems. Around 10–20% of patients admitted to hospital might be due to drug-related problems and adverse effects of drugs. The probability of drug-interactions is proportionate to the number of drugs prescribed (13). Patients with renal or liver disease, as well as the elderly are associated with higher chances of developing adverse reactions as a result of drug-drug interactions. Nonetheless, although possible drug- drug interactions may have impact on 40–65% of all admitted patients at the hospital, the clinical outcome of these interactions are inconsistent, and adverse effects hardly appear. A precise medication history is a crucial factor in the assessment of drug therapy (14).

The aim of this study was to reveal the prevalence and severity of potential drug-drug interactions among hospitalized psychiatric patients at the Psychiatry hospital in Sulaimani City.

Methodology

The current cross-sectional study involved 60 newly hospitalized psychiatric patients and data regarding the prescribed psychotropic drugs were collected. Data collection on each individual patient was performed on patient dossier to observe and report potential psychotropic drug interaction. The included psychiatric disorders that were frequently encountered included schizophrenia, bipolar disorder, psychosis, and major depressive disorder.

The data were recorded on a form of questionnaire that included patient's demographic data, all prescribed drugs, and patient's diagnosis. The drug interactions were evaluated and categorized, according to Medscape and BNF, into mild, moderate, and major.

Inclusion criteria:

1. Newly hospitalized psychiatric patients of all ages
2. Both males and females.
3. Patients receiving antipsychotic medications.
4. Patients who are mentally stable.

Exclusion criteria:

1. Irritable and uncontrollable patients.
2. Cases of addiction and drug overdose.

Primary outcome measure: Overall percentage of drug-drug Interaction, and percentage of different severities of interactions were regarded as primary measures.

Secondary outcome measure: Determine the percentage of most common prescribed psychotropic class of drugs.

Results

The average age of the population included in the current study was varied from 15 to 65 years with a mean of 39; both males and females were involved in the study (Table 1). Table 2 demonstrated that the association between psychiatric diseases and percentage of patients. The most frequently occurring psychiatric disease in the current study was bipolar disorder. The most frequently prescribed medications were antidepressants (Figure 1). Prevalence of potential drug-drug interactions reported in the psychiatric ward was 89 pairs of drug-drug interactions (98 %) (Figure 2), majorities of which were of moderate and severe (Table 3). Furthermore, (Table 3) shows the association between psychiatric diseases and drug interactions according to frequency and severity, highest percentage of the patients were diagnosed as depression (35%), patients with depression were reported to have a total of 25 drug-drug interactions. While bipolar disorder, schizophrenia, and psychosis were 29, 19, and 16 interactions respectively. Table 4 shows the total number of prescribed drugs per patient, most of the patients were prescribed at least 4-5 drugs. Tables (5,6, and 7) describe the pairs of drug-drug interactions between different psychotropic drugs with their mechanism of possible clinical consequence and frequency. In addition, the most frequent moderate drug interactions were (Diazepam co-administered with haloperidol, Procyclidine co-administered with haloperidol) which were repeated 43 and 34 times. The most frequent major drug interactions were (Escitalopram co-administered with Clomipramine and carbamazepine with clonazepam) which were repeated 3 and 4 times.

Table 1: Demographic characteristics

Age	Percentage of patients	Male	Female
15-24	(6) 10.0%	(4) 6.6%	(2) 3.3%
25-34	(18) 30.0%	(8) 13.30%	(10) 16.60%
35-44	(18) 30.0%	(8) 13.30%	(10) 16.60%
45-54	(9) 15.0%	(4) 6.60%	(5) 8.3%
55-64	(3) 5.0%	(3) 5.0%	(0) 0%
65	(6) 10.0%	(3) 5.0%	(3) 3.0%

Brackets represents number of patients, and % represents percentages

Table 2: Percentage of psychiatric diseases among male and female patients.

Disease type	Patients	Male	Female
Schizophrenia	(18) 30%	(10) 16.66%	(8) 13.33%
Major Depressive Disorder	(12) 20%	(2) 3.30%	(10) 16.66%
Bipolar Disorder	(21) 35%	(10) 16.66%	(11) 18.33%
Psychosis	(9) 15%	(4) 6.66%	(5) 8.33%

Brackets represents number of patients, and % represents percentages

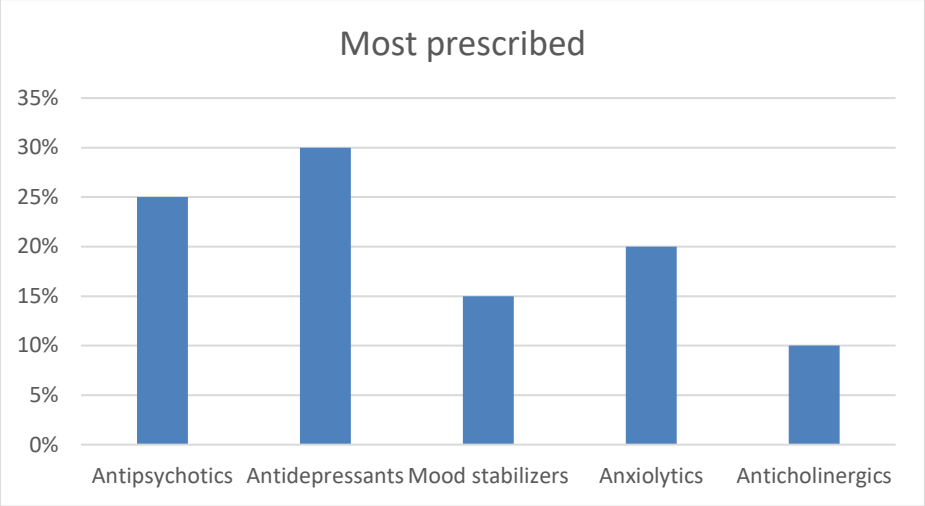

Figure 1: Percentage of the most prescribed medications

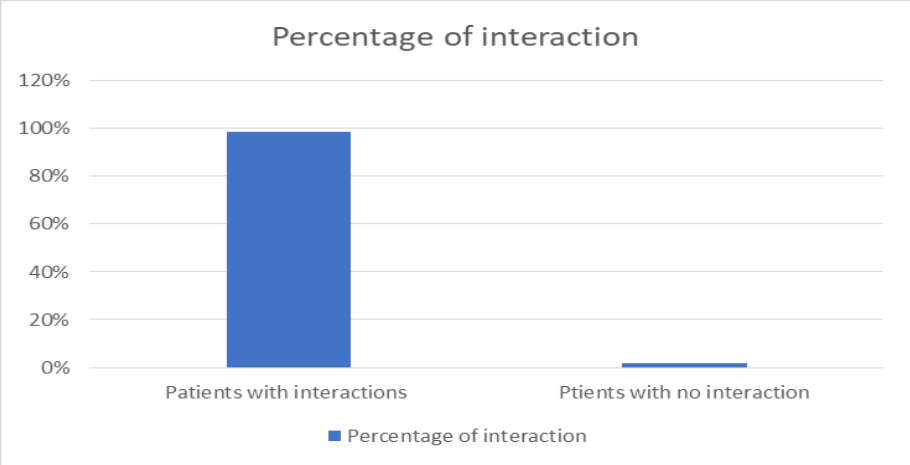

Figure 2: Prevalence of overall drug-drug interactions

Table 3: Association between psychiatric diseases and drug interactions according to frequency and severity

Disease	Patient number	Incidence of interaction				Row total
		Major	Moderate	Mild	No interaction	
Depression	(21) 35%	3	20	2	1	25 pairs of drug-drug interactions
Bipolar	(18) 30%	3	23	3	0	29 pairs of drug-drug interactions
Schizophrenia	(12) 20%	5	12	2	0	19 pairs of drug-drug interactions
Psychosis	(9) 15%	4	11	1	0	16 pairs of drug-drug interactions
	(60) 100%	15 (16.6%)	66 (73.3%)	8 (8.88%)	1 (1.1%)	89 pairs of drug-drug interactions

Brackets represents number of patients, and % represents percentages. Numbers not in brackets represent the numbers of different pairs of drug-drug interactions.

Table 4: Total number of drugs prescribed per patient.

Number (range) of prescribed medications per patient.	total number of patients
2-3	2
4-5	25
6-7	22
8-9	7
10-11	4

Table 5: Major drug-drug interactions between different psychotropic drugs with their mechanism of interaction and frequency.

Major drug-drug interactions	Drugs Interactions	Frequency	Possible outcome
Carbamazepine	Diazepam	1	Decrease the level of diazepam
	Clonazepam	3	Decrease the level of clonazepam
	Quetiapine	1	Decrease the level of quetiapine
Haloperidol	Amitriptyline	2	Increase QT interval
	Clomipramine	3	Increase QT interval Haloperidol will increase the level of clomipramine by affecting CYP2D6
	Citalopram	3	The level of haloperidol will be increased by affecting CYP2D6. Increased risk for serotonin syndrome or neurologic malignant syndrome and QT prolongation
	Fluoxetine	1	The level of haloperidol will be increased by affecting CYP2D6.
	Fluphenazine	1	Increased QT prolongation and anticholinergic effects
Clomipramine	Trihexyphenidyl	2	Effect of trihexyphenidyl is increased by pharmacodynamics synergism as well as the anticholinergic.
	Trifluoperazine	1	Increased QT prolongation and anticholinergic effects.
	Escitalopram	4	Increase serotonin level
	Sertraline	2	Increase serotonin level
Escitalopram	Sertraline	2	Increase serotonin level
	Amitriptyline	1	Increase serotonin level
Amitriptyline	Fluoxetine	1	Increase serotonin level/ fluoxetine will increase level of amitriptyline by acting on CYP2C19

Table 6: Moderate drug-drug interactions between different psychotropic drugs with their mechanism of interaction and frequency.

Moderate drug-drug interactions	Drugs Interactions	Frequency	Possible outcome
Diazepam	Haloperidol	43	Increase sedation
	Quetiapine	22	Increase sedation
	Risperidone	9	Increase sedation
	Olanzapine	16	Increase sedation
	trifluoperazine	2	Increase sedation
	Lorazepam	13	Increase sedation
	Clonazepam	11	Increase sedation
	Chlordiazepoxide	19	Increase sedation
	Clomipramine	3	Increase sedation
	Citalopram	4	Increase sedation
	Amitriptyline	8	Increase sedation
	Fluoxetine	2	Increase sedation
Lorazepam	Haloperidol	13	Increase sedation
	Risperidone	3	Increase sedation
	Olanzapine	5	Increase sedation
	Chlordiazepoxide	4	Increase sedation
	Citalopram	2	Increase sedation
	quetiapine	5	Increase sedation
	clonazepam	2	Increase sedation
	clomipramine	2	Increase sedation
Clonazepam	Haloperidol	12	Increase sedation
	Quetiapine	10	Increase sedation
	Olanzapine	5	Increase sedation
	Fluphenazine	1	Increase sedation
	Risperidone	1	Increase sedation
	Chlordiazepoxide	1	Increase sedation
	Clomipramine	2	Increase sedation
	Amitriptyline	1	Increase sedation
Chlordiazepoxide	Haloperidol	15	Increase sedation
	Quetiapine	7	Increase sedation
	Olanzapine	9	Increase sedation
	Risperidone	1	Increase sedation
	Clomipramine	4	Increase sedation
	Citalopram	2	Increase sedation
	Amitriptyline	4	Increase sedation
	Fluoxetine	1	Increase sedation
Lamotrigine	Valproate	1	Increase level of lamotrigine
	Escitalopram	1	Will increase lamotrigine, CNS depressants effect and may enhance psychomotor impairment
Carbamazepine	Haloperidol	4	Level of haloperidol is decreased by inducing its metabolism
	Olanzapine	2	Level of olanzapine is decreased by inducing its metabolism
Haloperidol	Quetiapine	22	Increase sedation, prolong QT interval, and increase antidopaminergic effects including extrapyramidal side-effects and neurologic malignant syndrome.
			Increase sedation, prolong QT interval, and increase antidopaminergic effects

	Risperidone	7	including extrapyramidal side-effects and neurologic malignant syndrome
	Olanzapine	12	Increase sedation, prolong QT interval, and increase antidopaminergic effects including extrapyramidal side-effects and neurologic malignant syndrome
	Clomipramine	3	Increase sedation Increase sedation Increase QT interval
	Amitriptyline	2	Increase QT interval
	Escitalopram	4	Increases the level of haloperidol by affecting its CYP2D6 metabolism
	Sertraline	5	Increase sedation
	Fluoxetine	1	
Olanzapine	Risperidone	2	Increase sedation and antidopaminergic effects including extrapyramidal side-effects and neurologic malignant syndrome
	Clomipramine	2	Increase sedation
	Amitriptyline	5	Increase sedation
Quetiapine	carbamazepine	1	Carbamazepine decreases olanzapine level by affecting its CYP metabolism
	Risperidone	1	Increase sedation, QT interval, and antidopaminergic effects including extrapyramidal side-effects and neurologic malignant syndrome
	Olanzapine	2	Increase sedation and antidopaminergic effects including extrapyramidal side-effects and neurologic malignant syndrome
	Escitalopram	2	Increase QT interval
	Citalopram	2	Increase sedation and QT interval
	Clomipramine	1	Increase sedation
Sertraline	Clomipramine	2	Sertraline will increase level of clomipramine by acting on CYP2D6
Procyclidine	Haloperidol	34	Increased anticholinergic effects.
	Olanzapine	9	Increased anticholinergic effects.
	Quetiapine	14	Dizziness, drowsiness, confusion, impaired thinking, judgment and motor coordination. Same as Quetiapine

	Diazepam Lorazepam Clonazepam Risperidone	31 7 10 7	Same as Quetiapine Same as Quetiapine Increased anticholinergic effects.
Trihexyphenidyl	Amitriptyline	1	Together decrease cholinergic effects

Table 7: Minor drug-drug interactions between different psychotropic drugs with their mechanism of interaction and frequency.

Minor drug-drug interactions	Drugs Interactions	Frequency	Possible outcome
Valproic acid	Clonazepam	3	Possible risk of absence seizure
Trifluoperazine	Sertraline Diazepam Lorazepam Risperidone	1 2 1 1	Effect of trifluoperazine is increased by CYP2D6 inhibition Increased sedation. Increased sedation. Increased QT interval, sedation and anticholinergic effects.
Fluphenazine	Haloperidol	1	Effect of fluphenazine is increased by inhibiting CYP2D6
Trihexyphenidyl	Risperidone	1	Additional anticholinergic effect Sertraline will increase the level
Carbamazepine	Sertraline	1	Serum level of carbamazepine is increased

Discussion

Psychiatric patients have increased risk of drug-drug interactions relative to other patients and the reason behind this is the prescription of a large number of medications and complex regimens (15). The results of the presented study showed that the range of prescribed drugs per patient was 4 to 5 and 6 to 7 medications in 25 and 26 patients respectively, which explains the high percentage of available drug interactions. Such finding was in agreement with a study that showed patients taking a higher number of drugs are at high risk for drug-drug interactions to occur. Furthermore, the study revealed that patients with schizophrenia have higher risks of developing drug-drug interaction, and programs that detect those drug interactions are helpful in preventing them (3).

The current study revealed a high prevalence rate of drug-drug interactions which was mostly of moderate severity (73.3%). The prevalence of previous findings conducted at psychiatry settings worldwide that demonstrated 81.8% (15) and 68.9% (16) in Ethiopia, 64.8% in Pakistan(17), and 64.7% in United Arab Emirates (8).

Furthermore, the results of the current study revealed the percentage of major drug-drug interactions which was 16.6 %. According to a study that was conducted in Ethiopia, the prevalence of potential serious drug-drug interaction among psychiatric patients was 42.8% which was higher relative to our results (15).

The highest percentage of prescribed medications was antidepressants (30%) and antipsychotics (25%), which may explain the higher incidence of serious drug-drug interactions in patients suffering from depression and schizophrenia. Clomipramine and escitalopram combination were among the most

frequently prescribed antidepressants that result in major drug-drug interactions that may lead to an increase of serotonin level, and this increases the risk of developing serotonin syndrome which can be life threatening (18,19).

Drug interactions that originate from psychotropic medications may result in reduced efficacy which can influence the clinical outcomes of patients. Most drug-drug interactions related to psychotropic medications are either pharmacokinetic or pharmacodynamics types of interactions. For instance, the combination of clomipramine and haloperidol result in elevation in the serum level of clomipramine as a result of CYP2D6 inhibition property of haloperidol (20). Furthermore, carbamazepine induces the metabolism of drugs that utilize CYP2C and CYP3A isozymes for their metabolism, and also induces its own metabolism. As a consequence, drug-drug interactions are mostly encountered when carbamazepine is co-administered with another drug. The presented study shows that one the most frequently documented pairs of major interacting drugs were carbamazepine and clonazepam combination. A study conducted in Brazil found that clonazepam and carbamazepine was the most prevalent combination that has major severity of drug-drug interaction (21). Such combination results in decreasing the serum levels of clonazepam.

Several psychotropic drugs, such as antipsychotics and antidepressants, were known to cause QT interval prolongation. Prolongation of this interval may lead to a life-threatening ventricular tachyarrhythmia known as torsade de points (TdP) (22). The current study demonstrated that several combinations that lead to the fatal prolongation of QT period, including the combination of haloperidol with each of amitriptyline, clomipramine, citalopram and fluphenazine. Furthermore, the combination of clomipramine with trifluoperazine is also associated with the major drug-drug interaction of prolonging the QT period. One study conducted in Jordan by Bulatova *et al.*, in 2021, revealed that among 307 recruited patients, there was a high prevalence of psychotropic drugs polytherapy, which were evidently associated with QTc prolongation, like citalopram, selective serotonin reuptake inhibitors, and tricyclic antidepressants (23).

A systematic review performed in Germany in 2011 stated that when haloperidol is administered intravenously at high doses, it might be linked to a very high risk of a long QTc interval and/or TdP. This ventricular arrhythmia was also associated with the use of quetiapine, tricyclic and tetracyclic antidepressants, and selective serotonin reuptake inhibitors such as citalopram (24). In a study conducted in India in 2019, investigated the frequency of drugs that prolong the QTc interval and QT-prolonging drug–drug interactions among patients at a psychiatry unit, nearly half of patients (47.9%) were reported as receiving drugs that have the ability to cause TdP (25).

Patients need to be closely monitored for these adverse effects specifically when olanzapine is added with haloperidol. Haloperidol dose may need to be reduced. Concomitant use of haloperidol with procyclidine, which has been repeated in 34 patients in the current study, may result in enhanced anticholinergic effects such as constipation, sedation, and dry mouth. This combination should only be used when clearly recommended. Concurrent administration of haloperidol with fluphenazine may result in higher risk of cardiotoxicity including QT prolongation and cardiac arrest. Such combinations are preferred to be avoided, and if utilized, then close monitoring is essential (24). Combination of haloperidol with olanzapine or quetiapine may lead to increased sedation, prolongation of QT

interval. Moreover, they both increase antidopaminergic effects including extra-pyramidal side effects and neurologic malignant syndrome.

Teamwork between physicians and pharmacists is a very important approach in reducing drug related problems. The duties of a pharmacist involve activities of training and providing information to the patient on the appropriate use of the drugs, as well as adverse drug reactions and compliance. In every hospital, the pharmacist should contribute to proper treatment of patients and detect drug related problems such as drug-drug interactions (26). Pharmacist interventions is crucial in detecting and managing drug-drug interactions, which results in reductions in the rate of occurrence of drug-drug interactions and its subsequent consequences (27,28).

Conclusion:

Patients suffering from psychiatric disorder are at high risk of drug-drug interactions due to their exposure to chronic treatment and polypharmacy. Generally, the incidence of drug-drug interaction increases proportionally to the number of drugs prescribed. According to our study, patients with major depressive disorder are more prone to adverse drug- drug interactions due to the large number of prescribed drugs.

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Conflict of interest:

The authors declare there is no conflict of interest.

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