

# Assessment of potential drug interactions among psychiatric inpatients receiving antipsychotic therapy of a secondary care hospital, United Arab Emirates

Haneen A.R. Aburamadan,  
Sathvik Belagodu Sridhar,  
Talaat Matar Tadross<sup>1,2</sup>

Department of Clinical Pharmacy and Pharmacology, RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University, <sup>1</sup>Psychiatry, RAK College of Medical Sciences, RAK Medical and Health Sciences University, <sup>2</sup>Department of Psychiatry, Ibrahim Bin Hamad Obaidallah Hospital, Ras Al-Khaimah, UAE

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## ABSTRACT

The majority of the antipsychotic drugs are also known to interact with other co-administered drugs. Drug–drug interaction (DDI) reports among patients receiving antipsychotic medications are common. The study aims to identify the potential drug–drug, drug–tobacco, and drug–ethanol interactions associated with antipsychotics and significant predictors of potential DDIs (pDDIs). A prospective observational study was conducted among psychiatric inpatients receiving antipsychotic therapy and met the inclusion criteria that were reviewed for the presence of pDDIs using DRUGDEX-Micromedex database 2.0. The identified pDDIs were graded according to the severity and type of documentation. A total of 110 patients had a minimum of a single interaction, and the overall frequency of pDDIs reported was 64.7%. Of 158 pDDIs, 92 interactions (58.2%) were of major severity, while 66 interactions were of moderate severity (41.8%). Olanzapine with valproate (40 [25.3%]) was the most commonly documented pDDIs, followed by risperidone with valproate (20 [12.6%]). Olanzapine with tobacco (20 [69%]) was the most common drug–tobacco interaction. Simultaneously, olanzapine with ethanol was the most common potential drug and ethanol interaction (9 [50%]). Variables such as the number of drugs and polypharmacy statistically significantly predicted pDDIs ( $F[7, 162] = 8.155, P < 0.05, R^2 = 0.26$ ). Knowing the severity of different pDDIs will help clinicians and prescribers monitor patient safety through regular monitoring for interactions and adverse drug effects in future. The number of medications and polypharmacy was found to be the most significant predictor of pDDIs.

**Key words:** Antipsychotics drug interactions, drug–drug interaction, drug–ethanol interaction, drug–tobacco interaction

### Address for correspondence:

Dr. Sathvik Belagodu Sridhar,  
Department of Clinical Pharmacy and Pharmacology, RAK  
College of Pharmaceutical Sciences, RAK Medical and Health  
Sciences University, Ras Al-Khaimah, UAE.  
E-mail: sathvik@rakmhsu.ac.ae

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## INTRODUCTION

A drug–drug interaction (DDI) has occurred when the effects of one drug are changed after the concomitant administration of another drug, leading to synergistic, additive, or antagonistic effects.<sup>[1]</sup> DDIs are known to be one of the common causes of increased hospital admissions,

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length of hospital stays, treatment cost, morbidity, and mortality.<sup>[2,3]</sup> DDIs can be a crucial factor for the occurrence of adverse drug reactions (ADRs) and adverse drug events.<sup>[4]</sup> Earlier studies have stated that 5% of the ADRs in hospital settings are because of DDIs,<sup>[5]</sup> while DDIs are likely to be the contributing factor for about 3-26% of ADRs requiring hospitalization.<sup>[6]</sup>

Potential DDIs (pDDIs) are those interactions, which can be predicted from the known pharmacological actions of the drugs and have the possibility to alter the effects of the co-administered drug.<sup>[7,8]</sup> Conversely, all pDDIs may not necessarily contribute to clinically significant or actual DDIs. However, pDDIs may need closer monitoring.<sup>[8]</sup> Various pharmacoepidemiological studies conducted in the different parts of the world in various study settings, study design, duration, and diverse population and with various DDI assessment tools have reported the prevalence rates of pDDIs, varying from 5% to 91%.<sup>[9,10]</sup>

Based on the underlying mechanism, DDIs are categorized as pharmacokinetic and pharmacodynamic interactions.<sup>[11]</sup> Patients suffering from psychiatric illness are at risk for DDIs because they are highly likely to receive chronic treatment using several medications to manage the signs and symptoms or due to medical and psychiatric comorbidity or multiple prescribers may be required in the management.<sup>[12,13]</sup>

Most antipsychotics are extensively metabolized by the hepatic cytochrome P450 enzymes. CYP1A2, CYP2D6, and CYP3A4 isoenzymes are of particular importance to the metabolism of antipsychotics. Consequently, the frequency of CYP mediated DDIs is found to be high in psychiatric patients.<sup>[14]</sup> Co-administration of inhibitors or inducers of these enzymes can lead to clinically significant adverse events or diminished clinical efficacy, respectively.<sup>[15-17]</sup>

Pharmacodynamic interactions are the most common interactions encountered in clinical practice.<sup>[17]</sup> Clinically, significant pharmacodynamic interactions may cause serious complications such as extrapyramidal symptoms (EPS), serotonin syndrome, QT prolongation, and seizure.<sup>[12]</sup> DDIs associated with antipsychotic medications may cause decreased efficacy and/or poor tolerability affecting the clinical outcomes.<sup>[12]</sup>

Demographic and treatment variables such as age, gender, primary diagnosis, number of medications received, or polypharmacy have shown a significant association with the occurrence of pDDIs.<sup>[18,19]</sup> There are few studies assessing solely the nature of pDDIs in psychiatric settings.<sup>[20-22]</sup> Tobacco smoking is common among patients receiving psychotropic medications, consequently reducing the plasma concentrations of the drugs,<sup>[23]</sup> while enhanced

central nervous system suppression resulting in impaired concentration, coordination, hypotension, and increased sedation is documented with alcohol and antipsychotics.<sup>[24]</sup>

Studies documenting pharmacoepidemiology of pDDIs among psychiatric disorder patients of the UAE are scarce. The primary aim of the study was to identify the pDDI, drug-tobacco, and drug-ethanol interactions associated with antipsychotics. The study also aims at analyzing the frequency, types, severity, and documentation grades of pDDIs and to identify the significant predictors of pDDIs.

## MATERIALS AND METHODS

This was a prospective observational study carried out in an inpatient psychiatric setting. We initiated the study after the approval from the Institutional and Regional Research and Ethics Committee approval (8-2015-PG-P and RAKREC-Aug-2015-3). The duration of the study was 7 months. The required sample size was 169, with a confidence level of 95%, a margin of error of 5%, and the population proportion of 50%.

Psychiatric inpatients of either gender, aged >13 years, and hospitalized in the psychiatry ward over 24 h were included in the study. Furthermore, we included patients diagnosed with any psychiatric disorder and managed with at least one antipsychotic medication. The study investigators identified the cases by attending ward rounds on alternative days (3 days/week) at the study site along with the treating psychiatrist.

We collected the required data from the electronic medical records of patients and entered into a data collection form designed for the study. The pDDIs were identified using DRUGDEX-Micromedex database 2.0.<sup>[25]</sup> The drugs, which are concomitantly received by the patients, were entered into the database for screening the presence of pDDIs. The database screens for pDDIs and above classifies pDDIs according to severity and documentation. The prescription-related polypharmacy was evaluated and categorized as minor, moderate, and major using Veehof *et al.* Scale.<sup>[26]</sup>

SPSS version 24.0 (IBM, New York, USA) was used to analyze the data. Descriptive statistics were used to evaluate the data. We assessed comparisons between categorical variables using the Chi-square test. A Pearson correlation was done to estimate the relationship between continuous variables and its association with the number of pDDIs. The odds ratio (OR) was also calculated. Multiple regression analysis was carried out to detect the predictors of pDDIs.  $P < 0.05$  was considered as statistically significant, further any value  $\leq 0.01$  was considered as highly significant.

## RESULTS

A total of 170 patients were included in the study and most of them were male (98 [57.6%]). The age of patients varied from 13 to 79 years, with a mean age of  $34.8 \pm 12.9$  years. A total of 78 (45.9%) of the patients were UAE nationals and the remaining were expatriate population. The length of hospital stay as inpatients varied from 2 to 74 days, with a mean length of stay of  $15.8 \pm 12$  days. A total of 52 (30.6%) patients had other comorbidities. Diabetes (18 [10.5%]) and hypertension (17 [10%]) were the most commonly documented comorbidities.

The majority of the study patients were nonsmokers (108 [63.5%]), also had no history of alcohol usage (141 [82.9%]). The mean number of medications received by the patients was  $2.69 \pm 1.09$ . The majority of the patients were categorized to have minor polypharmacy (114 [67.1%]), followed by moderate polypharmacy (34 [20%]), no polypharmacy (20 [11.80%]), and major polypharmacy (2 [1.2%]).

A total of 158 pDDIs were identified, quantified, and classified in 170 patients who got enrolled during the study period. Moreover, a total of 41 pairs of interacting drugs were recognized. A total of 110 patients had a minimum of a single interaction. The overall frequency of pDDIs among the study population was 64.7%. The predominance of pDDIs was documented in patients diagnosed with bipolar I disorder (29 [26.4%]), followed by schizophrenia (15 [13.6%]), schizoaffective disorder (14 [12.7%]), substance use disorder (10 [9.1%]), major depressive disorder 7 (6.4%), and alcohol use disorder (7 [6.4%]).

Olanzapine and valproate were the most commonly documented pairs of interacting drugs. The 10 most common pDDIs with their frequencies, severity, and documentation grade in the analyzed prescriptions are highlighted in Table 1.

Among the pDDIs identified, 92 (58.2%) were major and 66 (41.3%) were of moderate severity. The documentation grade of the predominance of the pDDIs was of fair (73 [46.2%]), followed by good (45 [28.5%]) and excellent (40 [25.3%]).

Among the 62 patients who were usual smokers of tobacco cigarettes, 29 (46.7%) patients were exposed to the interaction between antipsychotics prescribed during hospitalization and tobacco. All of them were males. Olanzapine was involved in the largest number of interactions with tobacco smoking (20 [69%]) [Table 2].

Among the 29 patients who were usual or heavy drinkers of alcohol, 18 (10.6%) patients were exposed to the interaction between antipsychotics prescribed upon discharge and alcohol. All of them were males. Olanzapine was involved in the largest number of interactions with alcohol (9 [50%]) [Table 3].

A statistically significant but weak positive linear correlation between duration of hospital stay and a number of DDIs ( $r = 0.158$ ,  $P = 0.039$ ) and a strong, highly significant positive association was documented between the number of drugs taking and the number of DDIs ( $r = 0.514$ ,  $P < 0.01$ ). The variables which were positively correlated with the risk of occurrence of pDDIs were length of hospital stay (OR: 0.440, 95% confidence interval [CI]: 0.216–0.893,  $P = 0.021$ ), number of drugs prescribed (OR: 3.266, 95% CI: 2.0–5.0,  $P < 0.01$ ), and polypharmacy (OR: 0.0049, 95% CI: 0.0001–0.3045,  $P < 0.05$ ) [Tables 4 and 5].

We ran multiple regression to predict the total number of pDDIs. It revealed that only variables such as the number of drugs and polypharmacy statistically significantly predicted pDDIs ( $F [7, 162] = 8.155$ ,  $P < 0.01$ ,  $R^2 = 0.261$ ). Number of drugs and polypharmacy added statistically significantly to the prediction,  $P < 0.01$ , as presented in Table 6.

**Table 1: Most frequent potential drug- drug interactions associated with antipsychotics**

Type of DDIs	n (%)	Severity	Documentation	Pharmacological consequences
Olanzapine- Valproate sodium	40 (25.3)	Moderate	Excellent	Decreased olanzapine plasma concentrations
Risperidone- Valproate sodium	20 (12.6)	Moderate	Good	Increased plasma valproic acid concentrations
Olanzapine- Quetiapine	11 (6.9)	Major	Fair	Increased risk of QT interval prolongation
Mirtazapine- Olanzapine	9 (5.6)	Major	Good	Increased risk of serotonin syndrome
Quetiapine- Risperidone	8 (5)	Major	Fair	Increased risk of QT interval prolongation
Carbamazepine- Quetiapine	6 (3.7)	Major	Fair	Increased carbamazepine exposure and risk for toxicity and decreased quetiapine efficacy
Escitalopram- Quetiapine	6 (3.7)	Major	Fair	Increased risk of QT interval prolongation
Diazepam- Olanzapine	5 (3.1)	Major	Good	Potential of excessive sedation and cardiorespiratory depression
Haloperidol- Quetiapine	4 (2.5)	Major	Fair	Increased risk of QT interval prolongation
Fluoxetine- Olanzapine	4 (2.5)	Major	Fair	Increased risk of QT interval prolongation

DDIs: Drug- drug interactions

**Table 2: Types of drug- tobacco interactions**

Type of interaction	n (%)	Severity	Documentation	Pharmacological consequences
Olanzapine- Tobacco	20 (69)	Major	Fair	Olanzapine levels probably decreased
Chlorpromazine- Tobacco	3 (10.3)	Moderate	Good	Decreased plasma chlorpromazine levels
Haloperidol- Tobacco	5 (17.2)	Major	Fair	Decreased exposure of CYP1A2 substrates
Clozapine- Tobacco	1 (3.4)	Major	Fair	Decreased exposure of CYP1A2 substrates

**Table 3: Types of drug- ethanol interactions**

Type of interaction	n (%)	Severity	Documentation	Pharmacological consequences
Olanzapine- Ethanol	9 (50)	Moderate	Fair	Excessive central nervous system depression
Quetiapine- Ethanol	8 (44.4)	Moderate	Good	Potential of the cognitive and motor effects of alcohol
Chlorpromazine- Ethanol	1 (5.6)	Moderate	Good	Increased sedation

**Table 4: Association between demographic and treatment-related variables and number of drug- drug interactions**

Variable	Occurrence of pDDIs, n (%)		$\chi^2$	P
	No	Yes		
Gender				
Male	34 (56.7)	64 (58.2)	0.037	0.848
Female	26 (43.3)	46 (41.8)		
Nationality				
UAE national	25 (41.7)	53 (48.2)	0.664	0.415
Expatriate	35 (58.3)	57 (51.8)		
Age (years)				
≤35	38 (63.3)	61 (55.5)	0.991	0.320
>35	22 (36.7)	49 (44.5)		
Length of stay (days)				
<15	46 (76.7)	65 (59.1)	5.292	0.021*
>15	14 (23.3)	45 (40.9)		
Presence of comorbidities				
Yes	17 (28.3)	35 (31.8)	0.222	0.637
No	43 (71.7)	75 (63.6)		
Number of drugs prescribed				
≤2 drugs	44 (73.3)	32 (29.1)	30.742	0.000**
>2 drugs	16 (26.7)	78 (70.9)		
Polypharmacy				
No polypharmacy	20 (33.3)	0 (0.0)	42.988	0.000**
Minor polypharmacy	33 (55.0)	81 (73.6)		
Moderate polypharmacy	7 (11.7)	27 (24.5)		
Major polypharmacy	0 (0.0)	2 (1.8)		

\*P<0.05=Statistically significant, \*\*P<0.001 Statistically highly significant.  
pDDIs: Potential drug- drug interactions

study.<sup>[27]</sup> In contrast, other studies have reported a lower frequency (23%) and a higher frequency (77.9%) of pDDIs.<sup>[17,22]</sup> This variation in the reported frequency could be due to the variance in the study designs, sample sizes, and consideration of classes of pDDIs (from minor to contraindicated). In our study, a higher number of pDDIs were identified in bipolar I disorder patients, whereas, in contrast, a study reported higher rates of pDDIs in patients with depression.<sup>[17]</sup> This variation in the findings is attributed to the divergence in the type of study population included.

The most commonly identified pDDIs in our study were olanzapine and valproate sodium, followed by risperidone and valproate sodium. A similar type of study reported a combination of first-generation antipsychotic and second-generation antipsychotic (olanzapine and haloperidol) as the most common pDDI.<sup>[17]</sup> DDIs between olanzapine and haloperidol are known to increase the risk of developing EPS.<sup>[28]</sup> Other studies have documented most common pDDIs between haloperidol and trihexyphenidyl (72 [5.3%]),<sup>[21]</sup> amitriptyline and fluoxetine (24.5%),<sup>[22]</sup> and antipsychotics and beta-blockers.<sup>[29]</sup> The difference in these findings could be due to divergences in the study setting, duration, and mainly the study population included.

The mainstream of the pDDIs identified in our study was of major severity type, whereas Balen *et al.* documented 34 serious and 20 moderate pDDIs.<sup>[22]</sup> Another study reported 15.2% major and 84.6% moderate type of pDDIs.<sup>[30]</sup> The documentation grade of a majority of the pDDIs in our study was the fair type, whereas Ismail *et al.* reported 38 (4.6%) excellent; 548 (66.4%) good; and 239 (29%) fair type of pDDIs.<sup>[27]</sup>

**DISCUSSION**

The overall frequency of pDDIs documented in our study was in accordance with the findings of Ismail *et al.* (64.8%)

It is crucial to note that regardless of the prescriber’s knowledge about pDDIs of antipsychotics with other drugs, the benefit of these treatment regimens may outweigh the risks caused by DDIs, especially for patients with severe mental illnesses.<sup>[17]</sup> No serious clinical outcome caused

**Table 5: Predictors of potential drug- drug interactions**

Variable (reference)	OR	95% CI	P
Age (<35 years)			
>35 years	0.721	0.378- 1.375	0.322
Gender (female)			
Male	1.064	0.563- 2.009	0.850
Nationality (expatriates)			
UAE Nationals	1.302	0.690- 2.457	0.418
Length of stay (<15 days)			
≥15 days	0.440	0.216- 0.893	0.021*
Presence of comorbidities (no comorbidity)			
Yes	1.180	0.592- 2.354	0.640
Number of drugs (≤2 drugs)			
>2 drugs	3.266	2.098- 5.084	0.000**
Polypharmacy (no polypharmacy)			
Minor polypharmacy	0.0100	0.0006- 0.1706	0.0015*
Moderate polypharmacy	0.0067	0.0004- 0.1233	0.0008**
Major polypharmacy	0.0049	0.0001- 0.3045	0.0116*

\*P<0.05: Statistically significant, \*\*P<0.001: Statistically highly significant. OR: Odds ratio, CI: Confidence interval

**Table 6: Predictors of potential drug-drug interactions by multiple regression analysis**

Model	Unstandardized	SE	Standardized	t	Significance	95% CI for B	
	coefficients		coefficients			Lower bound	Upper bound
	B		β				
Constant	-0.331	0.507	-	-0.654	0.514	-1.333	0.670
Gender	0.023	0.124	0.013	0.182	0.856	-0.222	0.267
Age	0.005	0.005	0.069	0.942	0.347	-0.005	0.015
Nationality	-0.037	0.126	-0.021	-0.295	0.601	-0.197	0.338
Presence of comorbidities	-0.136	0.141	-0.070	-0.964	0.337	-0.415	0.143
Number of drugs	0.538	0.149	0.300	3.604	0.000**	0.243	0.833
Polypharmacy	0.379	0.128	0.253	2.956	0.004*	0.126	0.632

\*P<0.05: Statistically significant, \*\*P<0.001: Statistically highly significant. CI: Confidence interval, SE: Standard error

by pDDIs was detected in our study. Therefore, all the interactions documented were of possible nature according to recent clinical studies.

It is worthy to mention that patients on antipsychotic therapy who are regular tobacco users may need higher doses of antipsychotics than nonsmokers.<sup>[31]</sup> This is because of the induction in the activity of human cytochromes P450 (CYP) 1A2 and 2B6, which metabolizes several antipsychotics, lowering their expected plasma concentrations.<sup>[15,32]</sup> Conversely, upon smoking cessation, tobacco users may require a decrease in the dosage of antipsychotics.<sup>[31]</sup> Among the 29 patients who were usual or heavy drinkers of alcohol, 18 (10.6%) patients were exposed to the interaction between antipsychotics prescribed upon discharge and alcohol. All of them were males. Consistently, Green *et al.* reported that 21% of patients with a history of alcohol abuse are less likely to respond to antipsychotics compared with people without the alcohol abuse disorder.<sup>[33]</sup>

A number of medications prescribed and polypharmacy were the significant predictors of the occurrence of pDDIs

in our study, since many psychiatric patients are expected to receive multiple medications due to the presence of some additional comorbidities along with their psychiatric illnesses.<sup>[12]</sup> In accordance with our findings, Oesterhus *et al.* documented the number of medications as the most significant predictor of DDIs in patients with mild dementia,<sup>[34]</sup> while other studies reported predictors such as prescribed medications,<sup>[22]</sup> race and female sex,<sup>[28]</sup> and patient's age.<sup>[21]</sup>

The primary limitation of our study was it was a single center-based study with a limited sample size and short study duration. Hence, the findings of this study cannot be completely generalized. The frequency, severity, and documentation grades of pDDIs solely dependent on the single analyzing software, i.e., Micromedex. Studies have documented variation in the frequency and nature of pDDIs with different drug interaction analyzing softwares. In addition, a good number of patients included in the study were not receiving other medications apart from psychotropic medications.

## CONCLUSION

The study necessitates the importance of continuous patient monitoring to identify the adverse events and careful selection of therapeutic alternatives if feasible. The pharmacist can contribute significantly in educating the patients or their family members regarding DDIs, polypharmacy, ADRs, and assessing the patient medication history. Further multicenter studies are required to substantiate the findings of our study.

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## Conflicts of interest

There are no conflicts of interest.

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