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# Drug-drug interactions and pharmacists' interventions among psychiatric patients in outpatient clinics of a teaching hospital in Saudi Arabia

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ABSTRACT

*Background:* Lack of recognition of labeled drug-drug interactions (DDIs) is a type of medication error of particular relevance to the treatment of psychiatric patients. Pharmacists are in a position to detect and address potential DDIs.
*Objective:* This study aimed to explore pharmacists' role in the identification and management of DDIs among psychiatric patients in psychiatric outpatient clinics of a university-affiliated tertiary care hospital in Riyadh, Saudi Arabia.
*Method:* This study was a retrospective, cross-sectional medical chart review of patients visiting outpatient psychiatric clinics. It utilized medical records of patients who were taking any psychotropic medications and were prescribed at least one additional drug. The hospital Computerized Physician Order Entry system was used to identify DDIs and determine the pharmacists' interventions. The Beers criteria were applied to detect inappropriate prescribing among older patients.
*Results:* On average, the pharmacists intervened in 12 out of 213 (5.6%) cases of major or moderate DDIs. Older age, higher number of prescription medications, the severity of DDIs, and the utilization of lithium and anticoagulants were positively associated with the pharmacist undertaking an action.
*Conclusion:* Future studies should explore the prevalence rate of harmful DDIs among psychiatric patients on a large scale and examine the effectiveness of different pharmacy policies in the detection and management of DDIs.
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## 1. Introduction

A medication error is defined as "an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient" (Goedecke et al., 2016). Medication errors comprise of mistakes in prescriptions, use of drugs not authorized by the prescriber, incorrect dosage, wrong dosage form, use of expired medications, and failure to use available data to monitor toxicity or interactions between drugs (The American Society of Health-System Pharmacists, 1993; Aronson, 2009; Wittich et al., 2014). It is important to recognize that "harm to the patients" includes not only the presence of adverse effects but also a lack of benefit from the treatment (Aronson, 2009). In addition to health risks associated with medication errors, their economic burden can reach over $100,000 per case (Walsh et al., 2017).

In the European system of collecting reports for the purpose of safety monitoring, EudraVigilance (Goedecke et al., 2016), only 242 of 28,338 cases of medication errors in general, i.e., less than 0.1%

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involved errors that result in harm (serious and non-serious) due to the lack of recognition of labeled drug-drug interactions (DDIs). Although one might argue that this is a small fraction, DDI-related errors may lead to substantial harm in special populations such as psychiatric patients. This group is not only at a higher risk for medication errors (Grasso et al., 2003; Bates et al., 2003; Gurwitz et al., 2000), but the potential for the DDI errors is magnified by additional hazards characteristic of this group, such as comorbidities, polypharmacy, and advanced age (Gurwitz et al., 2000; Felker et al., 1996; Sternberg, 1986; D'Mello et al., 1995; Joint Commission on Accreditation of Healthcare Organizations, 1999; Grasso and Bates, 2003; Nath and Marcus, 2006; Haw et al., 2007). In a study that explored the incidence and preventability of adverse drug events among geriatric patient population in 18 different community-based nursing homes in Massachusetts, almost 48% of the 546 detected adverse drug events were attributable to psychoactive agents (antipsychotics, antidepressants, and sedatives/hypnotics) (Gurwitz et al., 2000). Psychiatric medications also accounted for approximately 48% of all reported adverse drug events according to a study that investigated the rate of adverse drug events among psychiatric patients in a psychiatric hospital in the United States (Thomas et al., 2010). In addition, these DDIs can be life-threatening as suggested by a study that reviewed the medical charts of 240 psychiatric patients in a tertiary care hospital in Ethiopia (Mezgebe and Seid, 2015). Moreover, it was suggested that medication errors in mental health care services are under-reported in the literature and might be significantly more common than they appear to be (Maidment et al., 2006).

The incidence rate of medication errors is increasing worldwide and has been examined in multiple studies (Wittich et al., 2014; Bates et al., 2003; Gurwitz et al., 2000; Felker et al., 1996; Sternberg, 1986; D'Mello et al., 1995; Joint Commission on Accreditation of Healthcare Organizations, 1999; Grasso and Bates, 2003; Nath and Marcus, 2006; Haw et al., 2007; Thomas et al., 2010; Mezgebe and Seid, 2015; Maidment et al., 2006; de Vries et al., 2008; Lewis et al., 2009; Keers et al., 2013). The role of pharmacists in preventing these errors has been documented (Wang et al., 2015; Klopotowska et al., 2010; Langebrake and Hilgarth, 2010; Leape et al., 1999). However, only few reports are available concerning the magnitude of medication errors or the impact of pharmacists' interventions on their detection and management among psychiatric patients or in a mental health care setting (Haw et al., 2007; Maidment et al., 2006; Mann et al., 2008; Procyshyn et al., 2010). This scarcity of information and the need to address this issue was highlighted by the American Psychiatric Association (APA) Task Force on Patient Safety; the issued statement emphasized the importance of identifying, reporting and preventing medication errors in this underserved population (American Psychiatric Association Task Force on Patient Safety, 2003).

Typically, psychiatric patients suffer from multiple comorbidities besides their mental illnesses (Alosaimi et al., 2017). The need to treat more than one condition puts them at a significantly higher risk of DDIs and its detrimental consequences such as arrhythmia and death (English et al., 2012). These detrimental consequences of DDIs are most often due to changes in the pharmacokinetic or pharmacodynamic characteristics of the prescribed medications (Leucuta and Vlase, 2006; Ereshefsky, 2009). Based on their severity, DDIs are categorized as major (i.e., requiring a medical intervention to avoid life-threatening outcome or to minimize serious adverse events), moderate (i.e., resulting in an exacerbation of the patient condition and requiring change in the current therapy), and minor (i.e., leading to an increase in the frequency of side effects and requiring only patient counseling) (Aronson, 2007; Hoeft, 2014). As with the detection of other medication errors, the pharmacists' interventions in detecting and responding to DDIs is crucial in optimizing patient care and preventing severe adverse drug events (Busa et al., 2018; Balling et al., 2015; Moura et al., 2012; Bedouch et al., 2008).

To the best of our knowledge, the prevalence of DDI-related medication errors among psychiatric patients in Middle Eastern countries has not been investigated. Thus, the aim of the present study was to explore the involvement of pharmacists in the identification and management of the potential harmful DDIs among patients in the outpatient psychiatric clinics of a tertiary academic hospital in Riyadh, Saudi Arabia.

## 2. Materials and methods

This retrospective, cross-sectional chart review study utilized electronic medical records of patients visiting any of the outpatient psychiatric clinics at a university-affiliated tertiary care hospital in Riyadh, Saudi Arabia, between July and October 2016. Patients who were taking any psychotropic medications (e.g., antidepressants, antipsychotics, lithium, valproic acid, lamotrigine, carbamazepine), prescribed at least one additional drug, and had active electronic medical records, were included in the study. Patients who did not meet these criteria were excluded.

The medical city has implemented a Computerized Physician Order Entry (CPOE, Cerner Multum™, North Kansas City, MO, USA) in 2015. This system enables the physicians to send prescriptions electronically to the pharmacy department and allows physicians and pharmacists to request a DDI report for each patient. The CPOE software categorizes the severity of DDIs as major, moderate, or minor, or reports the lack of DDIs. The information about the possibility and seriousness of DDIs, and the actions taken by the pharmacists were extracted from the CPOE data. In addition, the American Geriatrics Society Beers criteria which list medications that should not be given, or given only with caution, to elderly patients were considered to detect inappropriate drugs prescribed for patients aged 65 years and older (American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015). According to the hospital policy and procedures, all interventions of pharmacists should be documented in the patient electronic medical record.

Chi-square and Fisher's exact tests were performed as appropriate to examine the differences in frequencies of pharmacists' interventions across the DDI severity categories as well as Beers criteria. Pearson's correlation coefficient was used to examine the association between the pharmacists' interventions and patients' age, gender, number of prescription medications, severity of DDI (major, moderate, minor, and none), and the utilization of different psychotropic and non-psychotropic drug classes. For the purpose of this study, the following actions were considered as pharmacists' interventions: contacting the prescriber and providing information on the detected drug interactions and their severity, contacting the prescriber and recommending adjustment of the dose, contacting the prescriber and recommending discontinuation of one or more medications, contacting the prescriber and recommending switching to another medication with better safety profile, and contacting the prescriber and recommending that the patient should be counseled about the potential increase in the frequency of side effects or that new side effects may be experienced. The minimum sample size was estimated to be 266 patients for a chi-square test at $\alpha = 0.05$, $\beta = 0.2$, power of 0.8, and medium effect size ($w = 0.22$), which was deemed to be sufficient to detect DDIs among psychiatric patients based on previously published studies (Mezgebe and Seid, 2015). All statistical analyses were performed using SAS® software, version 9.2. (SAS Institute Inc., Cary, NC, USA). The study was approved by the IRB of the College of Medicine at King Saud University.

## 3. Results

Medical records of 413 patients were reviewed; 270 of them were found to fulfill the inclusion criteria, and their characteristics are summarized in Table 1. Females constituted the majority of the study subjects. A wide range of ages was represented, with a mean of 38 years. There were 13 elderly patients (≥65 years) in which Beers criteria can be applied to. The patients received on average more than five medications, including those indicated for their psychiatric disorders. Multiple psychiatric diseases were represented, with major depressive disorder being the most frequently reported.

Among the 270 medical charts reviewed, the CPOE software detected 87 (32.2%) instances of major and 126 (46.7%) instances of moderate DDI (Table 2). There were also 4 (1.5%) cases of minor DDIs, and no DDIs were identified in 53 reports (19.6%). On average, the pharmacists undertook interventions in 12 out of 213 (5.6%) cases of major or moderate DDIs; no action was taken when minor DDIs were present. The pharmacists' interventions consisted of only dose adjustments and patient counseling and no prescription drugs were discontinued.

To detect possible associations between the pharmacists' interventions and other identifiable variables in the medical record, Pearson's correlation coefficients were utilized (Table 3). Patient's age, number of medications he/she was prescribed, the severity of DDIs reported by the CPOE system, and lithium and/or anticoagulants utilization were positively associated with the pharmacists' interventions. Conversely, no association was found between the patient gender and the pharmacists' interventions.

## 4. Discussion

The present study represents the first effort to define the impact of pharmacists on the identification and reporting of DDIs in an outpatient psychiatric health care setting in Saudi Arabia. The major finding of this investigation was that pharmacy professionals intervened only in scant number of identifiable DDIs for psychiatric patients. The potential reasons behind this low level of pharmacists' interventions to prevent and manage harmful DDIs lie beyond the scope of this study, however, it might be hypothesized that the heavy workloads of pharmacists with unclear job description and responsibilities might have contributed to the low level of intervention (Chui and Mott, 2012).

Pharmacists' interventions were positively associated with older age, higher number of medications, high severity DDIs, and with the utilization of lithium and anticoagulants. These findings suggest that pharmacists may be more likely to review the medication charts and intervene to prevent potential DDIs among older adults and patients on multiple medications. This could be attributable to the fact that older adults are more prone to adverse drug events and DDIs because of their higher likelihood to have multiple comorbidities and be on multiple medications (Gurwitz et al., 2000; American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015). Furthermore, polypharmacy increases the risk

**Table 1**
Characteristics of the patients.

| Characteristic | Number of patients (n = 270) |
|---|---|
| **Gender** | |
| Male, n (%) | 116 (42.96) |
| Female, n (%) | 154 (57.04)* |
| **Age,** years; mean ± SD | 38.22 ± 15.37 |
| **Number of Prescription Medications,** mean ± SD | 5.26 ± 4.00 |
| **Diagnosis** | |
| Major Depressive Disorder, n (%) | 40 (14.81) |
| Bipolar Affective Disorder, n (%) | 25 (9.26) |
| Schizophrenia, n (%) | 24 (8.89) |
| Obsessive Compulsive Disorder, n (%) | 12 (4.44) |
| Anxiety, n (%) | 10 (3.70) |
| Epilepsy, n (%) | 10 (3.70) |
| Generalized Anxiety Disorder, n (%) | 8 (2.96) |
| Attention Deficit Hyperactivity Disorder, n (%) | 7 (2.59) |
| Panic Disorder, n (%) | 6 (2.22) |
| Obnoxious Personality Disorder, n (%) | 3 (1.11) |
| Sleep Disorder, n (%) | 2 (0.74) |
| Social Phobia, n (%) | 2 (0.74) |
| Mania, n (%) | 1 (0.37) |
| Secondary Depression, n (%) | 1 (0.37) |
| Social Anxiety Disorder, n (%) | 1 (0.37) |
| Traumatic Brain Injury, n (%) | 1 (0.37) |
| Other**, n (%) | 117 (2.59) |

* Indicates statistically significant difference between males and females, $p = 0.02$.
** Hypomanic, unspecified depressive disorder, manic relapse, narcolepsy, specific phobias, unclassified diagnosis.

**Table 3**
Pearson's correlation coefficient, *r*, of the pharmacists' interventions and patients' age, gender, number of prescription medications, severity of DDI[a], and different drug classes.

| Variable | *r*-value | *p*-value |
|---|---|---|
| Age | 0.212 | 0.0004* |
| Gender | 0.083 | 0.175 |
| Number of Prescription Medications | 0.258 | <0.0001* |
| Severity of Drug-Drug Interaction | 0.904 | <0.0001* |
| ADHD Drugs Utilization | −0.042 | 0.488 |
| Anticonvulsants Utilization | −0.084 | 0.168 |
| Lamotrigine Utilization | −0.048 | 0.436 |
| Antihypercholesterolemic Agents Utilization | 0.112 | 0.066 |
| Antidiabetic Agents Utilization | 0.074 | 0.223 |
| Antihypertensive Agents Utilization | 0.102 | 0.095 |
| Selective Serotonin Reuptake Inhibitors (SSRIs) Utilization | −0.042 | 0.493 |
| Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) Utilization | −0.039 | 0.517 |
| Valproic Acid Utilization | −0.054 | 0.379 |
| Lithium Utilization | 0.405 | <0.0001* |
| Tricyclic Antidepressants Utilization | −0.036 | 0.551 |
| Anti-Asthmatic Agents Utilization | −0.029 | 0.629 |
| Carbamazepine Utilization | 0.021 | 0.732 |
| Over-the-Counter Drugs Utilization | −0.021 | 0.729 |
| Typical Antipsychotics Utilization | 0.016 | 0.791 |
| Atypical Antipsychotics Utilization | −0.008 | 0.906 |
| Anticoagulants Utilization | 0.206 | 0.0006* |

[a] Severity of DDI was categorized as major, moderate, minor, or none.
* Significant difference ($P < 0.05$).

**Table 2**
The pharmacists' interventions stratified by the severity of the DDIs and Beers criteria.

| | Type of DDI | | | | Beers Criteria | |
|---|---|---|---|---|---|---|
| | | Major (n = 87) | Moderate (n = 126) | Minor (n = 4) | Applicable (n = 13) | Not Applicable (n = 257) |
| Pharmacist's Interventions | Yes, n (%) | 5 (5.75) | 7 (5.56) | 0 (0.0) | 1 (7.69) | 14 (5.45) |
| | No, n (%) | 82 (94.25) | 119 (94.44) | 4 (100) | 12 (92.31) | 243 (94.55) |

of adverse drug events and DDIs (Grasso et al., 2003; Mezgebe and Seid, 2015). With regard to medications that are frequently implicated with preventable adverse drug events, lithium and cardiovascular medications such as anticoagulants were associated with most of the reported adverse drug events among hospitalized psychiatric patients according to a 3-year retrospective cohort study, and many of these reported adverse drug events were attributable to DDIs which could explain the positive association that was found in this study between pharmacist intervention and the utilization of lithium and/or anticoagulants (Thomas et al., 2010).

The identified rates of major, moderate, and minor DDIs, which were 32.2%, 46.7%, and 1.5%, respectively, are lower than the ones reported in another study that was conducted among psychiatric patients in Ethiopia (Mezgebe and Seid, 2015). With regard to the role of pharmacists in the identification and reporting of DDIs, a similar investigation was performed in an intensive care unit (ICU) at a hospital in Malaysia. This prospective case-control study determined that pharmacists' recommendations were made in approximately 16% of clinically significant DDIs (Hasan et al., 2012). Although the relative frequency of pharmacists' interventions was higher than that encountered in our study, it is still arguably low. These unfavorable situations occur despite the use of computerized systems, which are intended to help in the detection and prevention of DDIs (Classen et al., 2011; Yeh et al., 2014). The computerized systems facilitate the detection of potential DDIs, which in turn could prevent adverse drug events. However, the fact that pharmacists' interventions were only undertaken in a small number of major and moderate DDIs highlights the need to examine the possible reasons behind the low level of pharmacists' interventions to detect and manage preventable adverse DDIs.

Although the above-indicated values that are undoubtedly below the acceptable standard, the role of pharmacists in avoiding medication errors has to be appreciated. A systematic review of pertinent publications revealed that pharmacists' interventions could significantly decrease the occurrence of preventable adverse drug events and errors of prescribers (Wang et al., 2015). In another study that investigated the impact of pharmacists' interventions on reducing the rate of DDIs among psychiatric patients in Germany, the rate of interactions was reduced by 78% when pharmacists intervened (Hahn et al., 2013). Moreover, the rate of acceptance of pharmacists' interventions by physicians to prevent potential adverse drug reactions among patients in a psychiatric hospital in the United States was over 95% (Iuppa et al., 2013).

Studies evaluating the incidence of ADEs and medication errors in psychiatric inpatients in non-Western countries are scarce. An epidemiological study in psychiatric healthcare centers in Japan reported an incidence of 17.5 medical errors per 1000 patient-days (Ayani et al., 2016), but the specific information regarding the occurrence of DDIs was not made available. Similar studies in countries of the Middle East were not undertaken thus far and the current work begins to address this unmet need. In this regard, it has to be emphasized that studies investigating the role of community pharmacists in detecting DDIs in a non-hospital setting are urgently needed.

An important aspect of the current study is the methodology used for the collection of the data. It has been shown that the prevalence of medication errors is underestimated when data is gathered utilizing spontaneous self-reporting methods (Franklin et al., 2009; Meyer-Massetti et al., 2011). In contrast, the most effective means of estimating the prevalence of medication errors are the direct and prospective evaluations (Maidment et al., 2006; Dean and Barber, 2001). To the best of our knowledge, no studies were performed utilizing direct detection methods to ascertain the rate of medication errors due to DDIs in mental healthcare settings. The direct analysis of medical charts performed here strengthens the conclusions of our study. Furthermore, it is noteworthy that when Beers criteria were applicable among 13 elderly patients, only one pharmacists' intervention was made suggesting that not all pharmacists were aware of these criteria that should be followed when reviewing medication regimens of older adults (American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015). Therefore, providing continuous medical education on medication safety and appropriateness is necessary. Such continuous medical education programs and workshops to enhance patient safety must be provided regularly to all medical staff including pharmacists, and should be designed to enable pharmacists in particular to detect and manage DDIs in an interprofessional collaborative health care environment. Moreover, an institutional policy that does not only define the role of pharmacists in the detection and management of adverse drug events and DDIs, but also requires prescribers to cooperate with pharmacists in addressing such incidents should be in place to empower pharmacists to carry out their professional roles in ensuring patient safety.

## 5. Conclusion

The accumulated results indicate that there is an urgent need for creating a policy focused on the prevention of potentially harmful DDIs among psychiatric patients. In particular, the prescriptions for patients receiving multiple medications need to be verified and checked thoroughly, and the pharmacist dispensing these medications must ensure that the DDI report has been obtained. Also, quality improvement training programs for pharmacists and other healthcare providers should be implemented to improve the awareness of the serious consequences that may result if prescriptions are not examined for the possibility of harmful DDIs.

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