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Research Article

Common Neuropsychiatric Drug Interactions in Egypt That Require Clinical Interventions: A Retrospective Study in Delta Region

Mohamed Y Abdelgaied[1], Khloud Shendy[2], Omar Abdelmagged[2], Naira Galal[2], Mai Tarek[2], Abdalla Essa[2], Amr Zakaria[3], Noran El-tabakh[2], Hind Bakloul[2], Khaled Abdelkawy[4] and Michael G Zaki[5]*

[1]Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, T6G 2E1, Canada

[2]BSc of Pharmacy, Faculty of Pharmacy, Kafrelsheikh University, Kafrelsheikh, Egypt

[3]MSC of clinical pharmacy, Department of Clinical Pharmacy, faculty of pharmacy, Horus University, Gamasa, Egypt

[4]Assistant professor of clinical pharmacy, Department of Clinical Pharmacy, Faculty of Pharmacy, Kafrelsheikh University, Kafrelsheikh, Egypt

[5]Assistant professor of Pharmaceutical Sciences, School of Pharmacy and Health Sciences, Fairleigh Dickinson University, 230 Park Avenue, Florham Park, New Jersey, 07932, USA

***Corresponding author:** Michael G Zaki, School of Pharmacy and Health Sciences, Fairleigh Dickinson University, 230 Park Avenue, Florham Park, New Jersey, USA.

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Abstract

Background: Drug-drug interactions (DDIs) are a major concern in patients with complex therapeutic regimens. The increasing incidence of neuropsychiatric disorders gives more attention to neuropsychiatric drug interactions in clinical practice. However, limited reports of neuropsychiatric DDIs are available. This study aimed to identify neuropsychiatric DDIs that require clinical intervention in Egyptian outpatients' prescriptions.

Methods and Materials: An observational retrospective study was performed on Egyptian outpatients with different neuropsychiatric disorders in Delta region of Egypt. Prescriptions were analyzed for potential drug-drug using the Lexicomp® DDI database. Potential DDIs included both "D" and "X" risk ratings. Data were analyzed for incidence, Mechanism of action, major interacting therapeutic classes and outcomes. Descriptive statistics were used to calculate the incidence of a potential drug interaction.

Results: A total of 4341 outpatients' prescriptions were analyzed. Among them, 623 prescriptions were identified with at least one potentially interacting drug combination. The overall incidence rate of potential drug interactions was 14%. It was found that 86 prescriptions contained neuropsychiatric potential drug- drug interactions.

Conclusion: This increased incidence of neuropsychiatric DDIs shows that Egyptian outpatients are at a high risk of medication errors that can be prevented. This emphasizes the need for checking DDI during prescription writing and dispensing. In addition, providing DDI related information to the prescribers can play a vital role in minimizing the incidence rate of DDI.

Keywords: Neuropsychiatric; Drug Interaction; Lexicomp

Abbreviations: DDIs: Drug-drug interactions; ADRs: adverse drug reactions; COMT inhibitors: catechol-O-methyltransferase inhibitors; TCAs: Tricyclic Antidepressants; SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin and norepinephrine reuptake inhibitors; CYP450: Cytochrome P450

Introduction

With the increasing burden of patients with multiple disease states and drug combinations, pharmacotherapy has become more complex [1]. The polytherapeutic regimens increase the risk of drug-drug interaction (DDI) to a great extent. DDIs occur when the effect of one drug is altered by the concurrent administration of another medication. Drug interactions are not only attributed to interactions to other drugs but also natural supplements and food. Drug interactions can occur either by pharmacokinetic or pharmacodynamics mechanisms [2]. Pharmacokinetic drug interactions occur when the concurrently administered drug has a potential to alter one of the pharmacokinetic parameters; absorption, distribution, metabolism and excretion of the other drug [3]. On the other hand, pharmacodynamic drug interactions occur if concurrently administered drugs have agonist or antagonist effects for either therapeutic efficacy or adverse effects [3]. Outcomes from DDIs can lead to severe adverse drug reactions (ADRs) resulting in hospitalizations and life-threatening conditions. About 6-30% of all ADRs are attributed to DDIs [4]. Furthermore, ADR caused by DDIs accounts for about 2.8% of hospital admission every year in USA [5]. In addition, DDIs may result in diminished or increased therapeutic effect or adverse effects of one or both medications.

Recent treatment guidelines of neuropsychiatric disorders usually involve many therapeutic regimens [6]. The therapeutic classes for neurological disorders include dopamine agonists, catechol-o-methyltransferase "COMT" inhibitors and anticholinergic drugs for Parkinson's Disease and benzodiazepines and carbamazepine for epilepsy. In addition, the study involved some of the most common anti-depressants such as tricyclic anti-depressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and antipsychotics for bipolar disorders [6,7]. It is noteworthy that multiple drug administration increases the potential for significant drug interactions in clinical practice affecting both therapeutic efficacy and adverse drug events of medications [7,8]. However, there are no previous reports about the incidence of potential drug interactions with patients treated with medications for neuropsychiatric disorders in Egypt. Incidence and pattern of these DDIs in Egypt are not well-documented and little information is available. For this reason, this study aimed to identify the potential drug interactions with neuropsychiatric drugs for outpatients in Egypt giving insights about incidence, mechanisms, outcomes and major interacting therapeutic classes.

Methods

An observational retrospective study was performed on Egyptian outpatients who got their medications dispensed from Egyptian community pharmacies in Delta region of Egypt. The Delta region includes five Governorates "Kafrelsheikh, Menoufia, Gharbia, Damnhour, Dakahlia". Patients aged 18 years or older were included in the study. The study was approved by the Research Ethics Committee of Kafrelsheikh University according to Helsinki declaration. All participants gave their consent forms. Prescriptions were collected over a 12 months-period from January 1, 2020, till January 1, 2021, to ensure that drugs commonly prescribed in all environmental seasons are included. Neuropsychiatric and neurological disorders that were included in this study were epilepsy, Parkinson's Disease, Alzheimer's Disease, depression. Pharmacological classes for neurologic disorders included Anti-parkinsonian medications (dopamine agonist, catechol-o-methyltransferase "COMT" inhibitors and anti-cholinergic) and antiepileptic drugs (benzodiazepines, valproic acid, phenytoin, carbamazepine, gabapentin, pregabalin and piracetam). Pharmacological classes for psychiatric disorders that were included in the study include TCAs (amitriptyline, clomipramine), SSRI (citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), SNRIs (duloxetine) and hypericum perforatum for depression and anti-psychotic drugs (olanzapine, clozapine, quetiapine, chlorpromazine, and sulpiride).

Lexicomp Analysis: All prescriptions contained neuropsychiatric drugs were analyzed for potential drug-drug interactions using lexicomp® (Lexicomp, Inc., Ohio, USA) DDI database. In Lexicomp, a potential DDI can take a five-risk rating category from A, B, C, D and X which reflects both the level of urgency and the actions necessary to overcome the interaction. While category A has no reported drug interactions, category B and C are where there is a potential less serious DDI that does not require any action or to monitor therapy; respectively. Potential DDIs included in this report are either "D" and "X"-risk ratings since they include serious DDI that require modification of drug therapy or avoiding drug combinations; respectively. Data were analyzed for incidence, major interacting therapeutic classes, outcomes and mechanisms of actions.

Statistical analysis: Descriptive statistics were used to calculate the incidence of a potential dug interaction. All the statistical analysis was carried out with Statistical Package for Social Sciences (SPSS, IBM corporation version 16.0) considering $P < 0.01$ as statistically significant.

Result

Exactly 4341 prescriptions were included in the study and analyzed. Participants demographics were presented in the (Table 1).

Table 1: Basic Patients Demographic data.

	Incidence	
Age range	"36-71 years"	
Gender	Male	2632 (61%)
	Female	1709 (39%)

Governorate	Kafrelsheikh	1607 (37%)
	Gharbia	998 (23%)
	Menofia	187 (18%)
	AlQalyubia	521 (12%)
	Dakahlia	348 (8%)
Comorbid Disorders	Heart disorders	478 (11%)
	Liver disorders	391 (9%)
	Kidney disorders	304 (7%)
	Diabetes	289 (6.5%)

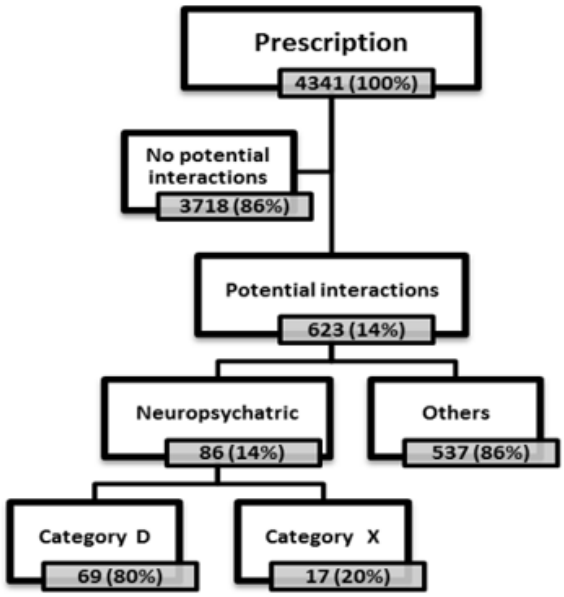

Figure 1: Incidence of potential drug interaction with neuropsychiatric drugs.

As revealed from (Figure 1), 623 potential drug interactions were identified. The overall incidence for potential drug-drug interactions was 14%. Only 86 potential interactions with neuropsychiatric drugs were reported (2% of the overall prescription). About 16 interactions for every one thousand prescriptions showed category D interactions. On the other hand, about 4 interactions for every one thousand prescriptions showed category X interactions.

(Table 2) shows the list of potential DDI with neuropsychiatric drugs "risk rating D or X". As shown from the table, the outcomes and mechanisms of drug interactions varied according to the nature of the drug.

Table 2: List of potential drug interactions with neuropsychiatric drugs.

Class	Neuropsychiatric drug A	Interacting drug B	Category	Outcomes	Mech.	Mechanism Description
Dopamine agonists	Pramipexole	Quetiapine	D	Decrease efficacy	PD	Quetiapine antagonizes action of dopamine agonist
	Bromocriptine	Pseudoephedrine	D	Toxicity	PD	Additive effects on blood pressure and vasoconstriction.
	Cabergoline	Sulpiride	X	Decrease efficacy	PD	They may antagonize each other's actions.
COMT inhibitors	Entacapone	Iron preparations	D	Decrease efficacy	PK	The possibility of chelation may result in decreased bioavailability.

Anti-cholinergic	Benztropine	Clozapine	D	Toxicity	PD	Additive anticholinergic effects leading to gastrointestinal hypomotility.
	Benztropine	Potassium chloride	X	Toxicity	PD	The risks of gastric and intestinal irritation and ulceration.
Benzodiaz	Alprazolam	Clarithromycin	X	Toxicity	PK	Inhibition of CYP3A4, an enzyme responsible for Alprazolam metabolism.
	Bromazepam	Oxomemazine	X	Toxicity	PD	Oxomemazine may enhance the CNS depressant effect of CNS Depressants (the risk of oversedation).
	Lorazepam	Valproic acid	D	Toxicity	PK	Valproate-mediated reduction in glucuronide metabolism of Lorazepam. Reduced serum clozapine concentrations due to induction of CYP450 by carbamazepine
Carbamaz	Carbamazepine	Clozapine	D	Toxicity/decrease conc.	PK +PD	Both carbamazepine and clozapine have been independently associated with neutropenia.
		Theophylline	D	Decrease efficacy	PK	Carbamazepine likely increases clearance of theophylline primarily via induction of its CYP1A2 mediated metabolism. The mechanism by which theophylline could decrease carbamazepine concentrations is unknown.
		Dexamethasone	D	Decrease efficacy	PK	CYP3A4 induction results in decreased dexamethasone exposure and effects.
		Clarithromycin	D	Toxicity/Decrease activity	PK	The ability of clarithromycin to inhibit CYP3A4. Carbamazepine induction of CYP3A4.
		Rivaroxaban	X	Decrease activity	PK	Induction of both CYP3A4-mediated metabolism and P-gp-mediated efflux of rivaroxaban.
Pregabalin	Pregabalin	Orphenadrine	X	Toxicity	PD	Additive or synergistic CNS depression due to the CNS depressant effects of orphenadrine.
Gabapentin	Gabapentin	Magnesium Sulfate	D	Toxicity	PD	The specific mechanism for the potential increase in CNS depression is unclear.
Valproic acid	Valproic Acid	Lorazepam	D	Toxicity	PK	Valproate-mediated reduction in glucuronide metabolism of lorazepam.
Topiramate	Topiramate	Thiazide	D	Toxicity/ increase conc.	PK+PD	The mechanism for this apparent drug-drug interaction is unknown.
Phenytoin	Phenytoin	Theophylline	D	Decrease efficacy	PK	The ability of phenytoin to induce CYP3A4 isoenzymes, and thus increase theophylline metabolism.
TCAs	Amitriptyline	Tizanidine	D	Decrease activity	PD	The mechanism for these interactions is not established.
	Amitriptyline	Orphenadrine	X	Toxicity	PD	Additive or synergistic CNS depression due to the CNS depressant effects of orphenadrine.
	Amitriptyline	Cisapride	X	Toxicity	PD	The risk of QT-interval prolongation and the increased possibility of pro-arrhythmia effects. Each agent has been independently associated with QT-prolonging effects.
	Clomipramine	Fluoxetine	D	Toxicity/increase conc.	PK+PD	Additional effects increase the risk for serotonin toxicity (also called serotonin syndrome). Fluoxetine-mediated inhibition of CYP2D6 and/or CYP2C19.
	Clomipramine	Dapoxetine	X	Toxicity	PD	(High Risk) additional effect increases the risk for serotonin toxicity (also called serotonin syndrome) a condition of serotonergic overstimulation characterized by autonomic, neuromuscular, and neurologic effects.

SSRIs SNRIs	Citalopram	Piroxicam	D	Toxicity	PD	The increase in bleeding described when these agents are combined likely results from a combination of NSAID-mediated reductions of gastroprotective prostaglandins and antiplatelet effects of both NSAIDs and SSRIs.
	Citalopram	Fluvoxamine	D	Toxicity/increase conc.	PK+PD	Inhibition of citalopram (and particularly S-citalopram) metabolism via CYP2C19. Additional effects increase the risk for serotonin toxicity (also called serotonin syndrome). The use of 2 SSRIs may also increase the risk for bleeding since these agents impair platelet function.
	Citalopram	Domperidone	D	Toxicity	PD	QT-prolonging Agents (Moderate Risk) may enhance the QTc-prolonging effect of Domperidone.
	Citalopram	Omeprazole	D	Toxicity	PK	Inhibition of Citalopram (and particularly S-citalopram) metabolism via CYP2C19, leading to increased Citalopram concentrations.
	Citalopram	Chlorpromazine	X	Toxicity	PD	QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Citalopram.
	Fluoxetine	Clomipramine	D	Toxicity/increase conc.	PK+PD	Additional effects increase the risk for serotonin toxicity (also called serotonin syndrome). Fluoxetine-mediated inhibition of CYP2D6 and/or CYP2C19.
	Dapoxetine	Clomipramine	X	Toxicity	PD	(High Risk) additional effect increases the risk for serotonin toxicity (also called serotonin syndrome) a condition of serotonergic overstimulation characterized by autonomic, neuromuscular, and neurologic effects.
	Duloxetine	Fluvoxamine	X	Toxicity/increase conc.	PK+PD	Inhibition of duloxetine metabolism via CYP1A2, leading to increased duloxetine concentrations. Additional effects increase the risk for serotonin toxicity (also called serotonin The use of Duloxetine and Fluvoxamine may also increase the risk for bleeding since these agents impair platelet function. syndrome).
Herbal	St. John's Wort	Omeprazole	X	Decrease efficacy	PK	St John's wort induction of CYP3A4 mediated omeprazole metabolism.
Anti-psychotics	Olanzapine	Sotalol	D	Toxicity	PD	QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Olanzapine.
	Clozapine	Carbamazepine	D	Toxicity/ Decrease conc.	PK+PD	Both carbamazepine and clozapine have been independently associated with neutropenia. Reduced serum clozapine concentrations.
	Clozapine	Benztropine	D	Toxicity	PD	Additive anticholinergic effects leading to gastrointestinal hypomotility.
	Quetiapine	Pramipexole	D	Decrease activity	PD	Opposing dopaminergic mechanisms of action.
	Chlorpromazine	Citalopram	X	Toxicity	PD	QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Citalopram leading torsade de point
	Sulpiride	Cabergoline	X	decrease activity	PD	They may antagonize each other's actions.
	Sulpiride	Magaldrate	D	decrease activity	PK	Antacids reduce the absorption of sulpiride.

Pk: Pharmacokinetics, PD: Pharmacodynamics, COMT: Catechol-o-methyl-transferase, CYP: Cytochrome, TCA: Tricyclic antidepressants, SSRI: selective serotonin reuptake inhibitors, SNRI: serotonin norepinephrine reuptake inhibitors Benzodiaz: Benzodiazepine, Carbamaz: Carbamazepine, NSAIDs: Non-steroidal anti-inflammatory drugs.

In addition, (Table 3) revealed the different mechanisms of neuropsychiatric drug interactions. Additive pharmacodynamic effects were the main mechanisms for interactions with antipsychotics and antidepressants. While metabolic inhibitions or induction of CYP450 were the main mechanisms for interactions with antiepileptic drugs.

Table 3: Mechanisms of neuropsychiatric drug interactions.

Interactions	Classification	Interacting drug combination
Pharmacokinetics	Absorption	• Entacapone + Iron preparations
		• Sulpiride + Magaldrate
	Metabolism	• Alprazolam + Clarithromycin
		• Lorazepam + Valproic acid
		• Carbamazepine + Clozapine
		• Carbamazepine + Theophylline
		• Carbamazepine + Dexamethasone
		• Carbamazepine + Clarithromycin
		• Carbamazepine + Rivaroxaban
		• Phenytoin + Theophylline
		• Clomipramine + Fluoxetine
		• Citalopram + Fluvoxamine
		• Citalopram + Omeprazole
		• Duloxetine + Fluvoxamine
		• St. John's Wort + Omeprazole
	P-glycoprotein efflux	• Carbamazepine + Rivaroxaban
Pharmacodynamics	Additive/ Synergism	• Bromocriptine + Pseudoephedrine
		• Benztropine + Clozapine
		• Benztropine + Potassium chloride
		• Bromazepam + Oxomemazine
		• Carbamazepine + Clozapine
		• Pregabalin + Orphenadrine
		• Gabapentin + Magnesium Sulfate
		• Topiramate + Thiazide
		• Amitriptyline + Orphenadrine
		• Amitriptyline + Cisapride
		• Clomipramine + Fluoxetine
		• Clomipramine + Dapoxetine
		• Citalopram + Piroxicam
		• Citalopram + Fluvoxamine
		• Citalopram + Domperidone
		• Citalopram + Chlorpromazine
		• Duloxetine + Fluvoxamine
		• Olanzapine + Sotalol
	Antagonism	• Pramipexole + Quetiapine
		• Cabergoline + Sulpiride
		• Amitriptyline + Tizanidine

The incidence of drug interactions with neuropsychiatric according to pharmacological classes was shown in (Figure 2). The three major therapeutic classes representing 85% of potential interaction were antidepressants, antiepileptic, and antipsychotic drugs 36%, 31%, and 18%, respectively [7-9]. Similarly, the three major pharmacological classes representing 50% of potential interactions were SSRI, antipsychotics, and carbamazepine 20%, 18% and 12%, respectively [8,10-12].

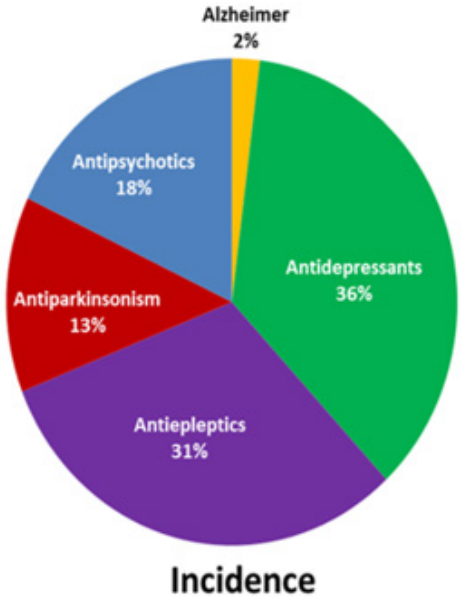

Figure 2: Neuropsychiatric therapeutic classes that show potential drug-drug interactions.

(Tables 4) showed major therapeutic classes of drugs that interact with neuropsychiatric drug. The three major therapeutic classes "represent 51% of potential interaction" were antipsychotics, muscle relaxants, and proton pump inhibitors 23%, 16%, and 12%, respectively. Consequently, these classes required more attention when prescribed with neuropsychiatric drugs to avoid any probable drug interactions.

Tables 4: Major therapeutic classes that interact with neuropsychiatric drug.

Therapeutic Class	Incidence (%)
Antipsychotics	23
Muscle Relaxants	16
Proton Pump Inhibitors	12
Anti-depressants	9
Anti-parkinsonism	7
Benzodiazepines	6
Ginko biloba	5
Antibiotics	4

Pearson correlation coefficient revealed that there was no significant correlation between reported risk factors "liver disorders, renal disorders, heart disorders, diabetes" and incidence and/or severity of drug interactions with neuropsychiatric diseases.

Discussion

Most neuropsychiatric patients take many drugs meaning many drugs per prescription in recent guidelines. This polypharmacy increases the likelihood of DDIs [7,13]. To our knowledge, this study was the first one that evaluates neuropsychiatric DDIs in Egyptian outpatients´ prescriptions. This study showed that that Incidence of potential neuropsychiatric DDIs in Egypt was 14% of neuropsychiatric DDIs. This study explored the importance of the preventive program to avoid potential medication errors in clinical practice and to avoid any hazardous effects of these interactions on Egyptian patients.

The major interacting classes were antidepressants, antiepileptic, and antipsychotic drugs. This shows the importance of giving more attention to these therapeutic classes in clinical practice. These classes require drug interaction evaluation with other concurrent drugs before dispensing their prescriptions. In pharmacy practice, the significant role of the pharmacist in checking prescription for any possible interaction with these therapeutic classes should be emphasized to prevent possible medication errors and avoiding any expected harmful outcomes [14].

As reported from this study, awareness of mechanisms of DDIs is very crucial to expect possible similar interactions with similar drugs in the therapeutic classes and whether the interactions are drug specific or class specific. In addition, being alert full of potential DDIs help suggest the possible alternative to avoid these interactions. This study showed that pharmacodynamic effects on dopamine and serotonin receptors were the main mechanisms for interactions with antipsychotics and antidepressants. While metabolic alterations of CYP450 mainly CYP3A4 were the main mechanisms for interactions with antiepileptic drugs.

Previous studies found similar results considering the association between patient characteristics and the prediction DDI. Abolhassani et al. studied 17,742 adult patients discharged between 2009 and 2015 from a department of internal medicine at Swiss hospital [15]. They found that age, number of comorbidities and a higher Charlson Comorbidity Index independently associated with polypharmacy. Similarly, Pérez et al. studied 38,299 patients in Ireland between 2012 and 2015 and found that age and multimorbidity were associated with a higher risk of DDI [15]. Furthermore, they found that hospital admissions themselves were independently associated with a higher risk of DDIs.

Limitations of this study include that these studies did not investigate psychiatric inpatients. To the best of our knowledge, there is currently no evidence comparable in scale and scope investigating the prediction of polypharmacy and the risk of DDI in hospital psychiatric units. Predicting other outcomes in hospitalized patients has often been found to be more complex in psychiatry than in other medical disciplines [16-18]. There are many reasons contributing to the difficulty of studying DDIs in psychiatric inpatients including less distinct diagnostic concepts, less standardization of care and a broader spectrum of acceptable therapeutic regimes [19-24]. Further studies are required to evaluate the DDIs in neuropsychiatric inpatients. In addition, prescription for pediatrics and more regions from different governorates of Egypt should be included in further studies. Also, natural supplements and herbal products including beverages and juices like green tea and grapefruit juices should be considered in further drug interactions evaluations [25-26].

Conclusion

Egyptian outpatients taking neuropsychiatric drugs are at a high risk of hazardous DDIs as revealed from the reported incidence from prescription. This emphasizes the need for the evaluation of potential DDIs during prescription writing to protect patients from harmful outcomes of drug interactions. In addition, providing DDI-related information to the prescribers and using drug interaction software programs to the dispensing pharmacist can play a vital role in minimizing the incidence rate of DDIs. The preventive program monitoring for interactions outcome and increasing awareness of potential drug interaction are recommended in clinical practice in Egypt.

Author contributions

Khaled Abdelkawy conceived of the research and study design and revised the manuscript. All authors contributed to data collection and statistical analysis. Mohamed Abdelgaied wrote the first draft of the manuscript. Michael G Zaki and Khaled Abdelkawy revised the manuscript. All authors read and approved the final manuscript.

Data availability

The data that support the findings of this study are available upon request from the corresponding author.

Acknowledgement

None.

Conflict of Interest

No Conflict of Interest.

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