EVALUATION OF POTENTIAL DRUG-DRUG INTERACTIONS IN PSYCHIATRIC PATIENTS: A PILOT STUDY

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ABSTRACT

INTRODUCTION: Drug-drug interactions (DDIs) are common but avoidable causes for adverse drug reactions.

AIM: The present pilot study aimed to assess the prevalence of potential DDIs (pDDIs) among patients with psychiatric disorders by evaluation of patients' hospital records and their discharge medication lists.

MATERIALS AND METHODS: A retrospective review of medication information was conducted for 47 male patients consecutively admitted for a period of one month to the acute unit of a university-based psychiatric clinic. Potential DDIs were checked with Medscape drug interaction checker and standard references on drug interactions, and were classified as major, moderate, or minor according to their severity. The statistical analysis included: Chi-square test, Student's t-test, and correlation analysis.

RESULTS: For the duration of the hospitalization a total of 121 interacting drug pairs were detected, potentially capable of inducing DDIs (2.57 per patient). Out of all the patients 44 (94%) were exposed to at least one pDDI and 7 (15%) to at least one serious pDDI. The most common potential risk was the additive sedative effect, involving 58 drug pairs with an average rate of 1.23 per patient. QTc prolonging drug combinations were found in 11 (23%) patients, drug combinations with potential risk of hematologic toxicity in 10 (21%) patients and such with potential risk of hepatic/metabolic toxicity in 9 (19%). CYP-mediated pDDIs were identified in 8 (17%) patients. At hospital discharge fewer pDDIs per patient (1.13) were detected.

CONCLUSION: A high prevalence of pDDIs among the psychiatric inpatients was recorded. Caution is warranted to limit the exposure of the patients to pDDIs.

Keywords: *potential drug-drug interactions, psychiatric patients, discharge medications*

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INTRODUCTION

Drug-drug interactions (DDIs) are among the most common causes for adverse drug reactions (ADRs). They constitute about 26% of the ADRs leading to hospital admissions (1). At the same time, they are a preventable medication-related risk to patients (2). Good knowledge of the mechanisms and the predisposing factors leading to DDIs is a prereq-

uisite to avoiding drug combinations associated with potential toxicity or inefficacy.

Based on their mechanisms, two major types of DDIs are distinguished: pharmacokinetic and pharmacodynamic. In general, the pharmacokinetic DDIs are considered to be more common and clinically relevant. These interactions occur when one drug alters the concentration of another drug with clinical consequences. The pharmacodynamic DDIs occur between drugs with additive or opposing effects and can result in significant toxicity or reduced effects. The brain is the organ most commonly compromised by pharmacodynamic interactions (3).

DDIs are not equally relevant for the clinical practice. According to the clinical severity of the potential result they are usually classified into three categories: serious or severe (drug combinations should generally be avoided whenever possible, as they can result in potentially serious toxicity or lack of efficacy), moderate (requiring an alteration in drug dosage or increased monitoring), and minor or mild (which have limited clinical impact and require no change of therapy).

Old age, polypharmacy, long hospital stays, gender, and comorbid conditions have been reported as common risk factors for DDIs (4).

Few studies have addressed the issue of DDIs in psychiatric wards (5-8). On the other hand, antipsychotics, antidepressants, and mood stabilizers are among the bulleted drugs listed in the drug interactions appendix of the British National Formulary, signifying 'interactions that are potentially hazardous and where combined administration of the drugs involved should be avoided' (9).

AIM

The aim of the present study, designed as a pilot clinical investigation, was to evaluate retrospectively the prevalence of potential DDIs (pDDIs) in male patients with psychiatric disorders both during their hospital stay and at discharge from a university-based intensive psychiatric unit, and to make a comparison of the exposure to pDDIs of the patients as inpatients and outpatients.

MATERIALS AND METHODS

This retrospective cross-sectional clinical investigation involved a sample of 47 adult male patients successively hospitalized in November 2016 in an intensive psychiatric unit of the University Hospital in Varna. The medical records of the patients were reviewed and the following data were collected: patient's age, length of hospital stay, psychiatric diagnosis, drugs prescribed during hospital stay and at discharge. To identify pDDIs, the free Drug Interaction Checker platform of Medscape and standard references on drug interactions were used.

DDIs were classified as major (serious, contraindicated), moderate or minor, according to their severity and as pharmacokinetic or pharmacodynamic according to their mechanism. The pDDIs were analyzed in respect to the exposure of the patients to certain potential risks or presumed organ toxicity.

Drugs known to have a low therapeutic index, to exhibit potentially severe side effects and to inhibit or induce drug-metabolizing enzymes, mainly cytochrome P450 (CYP) isoforms were given particular attention.

Data analyses: Chi-square test was used to compare the exposure to pDDIs during hospital stay and at discharge from hospital, with $p<0.05$ being considered as the level of significance. Student's t-test for comparison of two means and correlation analysis to identify the strength of relationships between variables were performed.

The study has been approved by the internal Ethical Committee of the Medical University of Varna.

RESULTS

The patient sample included 47 men aged 19-68 years (mean age 43.7, SD: ±12.5**).** The most common diagnosis was paranoid schizophrenia (22 patients), followed by bipolar affective disorder (11 patients). Seven patients were treated for psychic and behavioral disorders caused by alcohol or substance use with or without abstinence, 4 for a depressive episode, and 1 for dementia. One patient was diagnosed with moderate mental retardation and another with emotional instability with alcohol abuse.

Hospital length of stay ranged from 6 to 46 days, with a mean of 20 days.

A total of 175 of drugs were prescribed to the patients during the observed period. Out of these: 49 were antipsychotics, 42 – anxiolytics, 35 – anti-

epileptic drugs, 16 – antidepressants, 2 – anticholinergic drugs, 2 – cognitive enhancers and 1 – lithium. Administered occasionally were 28 non-psychotropic drugs intended to treat comorbidities.

Hospitalization period: Diazepam was the most frequently prescribed drug (35 patients), followed by sodium valproate (24 patients), and olanzapine (14 patients). These drugs were also most commonly involved in pDDIs.

A total of 121 pDDIs (2.57 per patient) were detected for the period of the hospital stay, and most of them – 103 (2.19 per patient) – were of moderate severity, followed by 9 (0.19 per patient) of serious severity and 9 of minor severity. Out of all patients 44 (94 %) were exposed to at least one pDDI and 7 (15%) of the patients received at least one drug pair with the potential to cause a serious adverse event.

Eleven drug pairs prescribed to the patients while hospitalized were associated with pDDIs, which could lead to QTc interval prolongation. Olanzapine, escitalopram, chlorpromazine, and clozapine were mainly involved in these drug combinations.

Drug pairs synergistic in causing blood dyscrasias were prescribed to 10 patients, with the drug combination being almost exclusively olanzapine and sodium valproate. The same drug pair is also associated with pDDIs that could result in increased liver enzymes and weight gain. Five drug pairs showed synergism leading to extrapyramidal side effects and two - to serotonin syndrome.

Pharmacokinetic pDDIs caused by changes in cytochrome P450 activity were detected in eight prescriptions, involving mainly carbamazepine and oxcarbazepine, as well as fluoxetine, paroxetine, duloxetine, haloperidol, and chlorpromazine.

Tabl. 1. Distribution of pDDIs based on their severity

Characteristics	Inpatients	Outpatients	p
Patients with at least one pDDI - overall	44/ 93.6%	24/ 51.1%	< 0.001
Patients with at least one serious pDDI	7/ 15.0%	3/ 6.4%	> 0.05
Patients with at least one moderate pDDI	44/ 93.6%	20/ 42.6%	< 0.05
N of pDDIs - overall/per patient	2.57	1.13	< 0.01
N of serious pDDIs/per patient	0.19	0.11	> 0.05
N of moderate pDDIs/per patient	2.19	0.91	< 0.01
N of minor pDDIs/per patient	0.19	0.11	> 0.05

N-number, pDDI - potential Drug-Drug Interactions

All pDDIs, except those associated with changes in cytochrome P450 activity – 8 (17%), were pharmacodynamic interactions. Most relevant to clinical practice were the synergistic pDDIs resulting in increased sedative effect, QTc interval prolongation, extrapyramidal side effects, and serotonin syndrome. Two of the pDDIs with pharmacokinetic mechanism were considered clinically relevant i.e. metoprolol overdose and reduced efficacy of diazepam.

Out of all pDDIs 58 (48%) resulted in potentially synergistic sedative effect of both drugs, represented by drug pairs prescribed to 42 patients (1.38 per patient). Diazepam was involved in 41 of these pDDIs that affected 35 patients.

Hospital discharge lists: 128 drugs were prescribed, among which 53 drug pairs were identified as leading to pDDIs (1.13 per patient). Most of them – 43 (0.91 per patient) – were of moderate severity, 5 (0.11 per patient) were of serious severity, and 5 were of minor severity. Out of the detected pDDIs in the discharge medication lists, only 6% were CYP-based.

Out of all patients at discharge, 24 (51%) were exposed to at least one pDDI, 23 (49%) of these to at least one moderate or serious pDDI. The ADRs that could result from the pDDIs at discharge were hematological ADRs (10 patients), QTc interval prolongation (9 patients) and sedation (6 patients).

The drugs involved most frequently in the pDDIs at discharge were olanzapine (16 pairs), valproate (10 pairs), aripiprazole and clozapine (7 pairs each), trazodone (6 pairs), escitalopram (4 pairs), etc.

The number of prescribed medications was the only factor significantly associated with the number of the detected pDDIs, both during the hospital stay (Pearson r=0.667; $p < 0.001$) and at discharge (Pearson r=0.727; $p < 0.001$). There was no significant association between the age of the patients and the length of the hospital stay with the number of the detected pDDIs in our study.

Psychiatric diagnosis tended to have an impact on the number of the detected pDDIs: for the hospitalization period the patients with bipolar disorder (n=11) had non-significantly higher number of pDDIs (3.18 per patient), compared to patients with paranoid schizophrenia (2.13 per patient). At discharge, however, the difference became significant (p=0.0007).

DISCUSSION

This was a pilot retrospective study aiming to assess the frequency and nature of pDDIs associated with pharmacotherapy of psychiatric disorders. Patients with such disorders are at particular risk for DDIs because of the practice of symptom-based prescribing, longer hospital stays and multiple prescribers, and medical, including psychiatric, comorbidity. DDIs contribute significantly to hospital admissions, treatment failures, avoidable medical complications, and subsequent healthcare costs (10, 11).

Our results show a high frequency of pDDIs among hospitalized psychiatric patients. Results very close to our data (96% pDDIs) were reported by Vasudev and Harrison (2008) in a study among hospitalized elderly psychiatric patients in Great Britain (5). However, Ismail et al. (2012) and Ocana-Zurita et al. (2016) reported a lower frequency of pDDIs among hospitalized psychiatric patients in Pakistan and Mexico, respectively (8,12).

The rate of the pDDIs for the patients at discharge in our study (51%) was significantly lower than that found for the period of the hospitalization. An epidemiological study on schizophrenic outpatients, based on prescriptions in a large US state's Medicaid claims database, revealed a rate of pDDIs of 23%, while in a mixed Turkish population of inpatients and outpatients with schizophrenia, a rate as high as 71% was reported (13,14).

The variation in the reported data may be attributed to a number of factors. An essential one is the different sources used in the studies to check the pDDIs. Vasudev and Harrison (2008) stressed this issue, using the results of their study to question the concordance of two well-referenced databases they had used (5). We have encountered similar problems with two other databases, choosing one of them in addition to other references.

Other factors influencing the rate of the pDDIs are the age of the study population, the psychiatric diagnoses of the patients, the mechanism of the evaluated pDDIs, and the study designs. The higher prevalence of pDDIs for the psychiatric inpatients in our study may be partly due to the entirely male sample, the acute setting of the patient unit, and the mode of prescribing associated with psychiatric emergencies. In their survey, Davies et al. (2004) focused on CYP-based pDDIs in two subgroups of patients – adults and elderly – and demonstrated a higher rate of pDDIs related to CYP3A4 for the functional elderly patients (6).

Paranoid schizophrenia was the psychiatric diagnosis in 47% of the patients in our study population. In part this could give an explanation for the different results of other studies focusing on schizophrenia only (13,14). Bipolar affective disorder was the diagnosis in 23% of the patients and these prescriptions actually accounted for a higher prevalence of pDDIs in our patient sample.

Mechanisms of the evaluated interactions are relevant to the reported results. The studies of Davies et al. (2004) and Guo et al. (2012) were focused exclusively on CYP-based pDDIs (6, 13), while in our research we were interested in both types of pDDIs: pharmacokinetic and pharmacodynamic. Out of all detected pDDIs for the period of the hospital stay in our study only 17% were CYP-based and for the discharge medications the rate was 6%. The pharmacokinetic pDDIs involved both inducers and inhibitors of cytochrome P450 enzymes as carbamazepine, oxcarbazepine, paroxetine, fluoxetine, duloxetine, haloperidol, and silymarin, prescribed in drug pairs with diazepam, valproic acid, aripiprazole, and metoprolol. The main CYP isoform involved was

CYP 2D6. Similar findings were reported by Davies et al. (2004) (6).

We determined the frequency and nature of the pDDIs for the same patient population in different clinical settings. The significant difference of the rate of the pDDIs during the hospital stay (2.57 per patient) and at discharge (1.13 per patient) ($p<0.01$) could be explained by the severity of the psychiatric conditions under treatment.

Analysis of the pharmacodynamic pDDIs showed exposure to certain potential risks regardless of the clinical setting in which they were identified such as additive sedative effects of the administered drugs, possible QTc prolongation, potential risk of hematologic toxicity and/or hepatic/metabolic toxicity. While the additive sedative effect was significantly more associated with the hospital stay than the discharge period ($p<0.01$), the risk of QTc prolongation was not significantly associated with the clinical setting. A prolonged QTc often arouses concern in clinical practice, as it can be followed by the life-threatening polymorphic ventricular tachyarrhythmia called torsade de pointes (TdP) (15). Psychotropic drugs are commonly associated with such kind of pDDIs, which fall under the category of moderate-to-serious interactions depending on the potential of the particular drug to prolong the QTc interval. The main drug pairs involved in our study were: escitalopram-olanzapine, haloperidol-chlorpromazine, clozapine-chlorpromazine, trazodone-ivabradine, quetiapine-escitalopram, amisulpiride-clozapine, olanzapine-lithium carbonate, olanzapine-mirtazapine, fluoxetine-olanzapine. It should be noted, however, that drug-induced QTc prolongation and/or TdP usually occur in patients with underlying risk i.e. age over 65 years, pre-existing cardiovascular disease, bradycardia, female sex, hypokalemia, hypomagnesemia, high therapeutic or toxic serum concentration of the prescribed drug, often in the setting of polypharmacy or the simultaneous administration of other drugs that delay repolarization or interfere with drug metabolism (15,16). Thus, it is strongly recommended that the concomitant use of medications known to prolong the QTc interval should be avoided in vulnerable patients (15-17). Aripiprazole appears to be the safest alternative among the atypical antipsychotics in terms of cardiotoxicity and should be considered in cases of increased risk of rhythm disorders (17).

Psychotropic drugs can cause a variety of blood dyscrasias, although it is still difficult to estimate the true prevalence of such risks (18). The pDDIs associated mainly with a risk of thrombocytopenia in our study were linked especially to the drug pair of olanzapine/valproic acid. An early review on hematological side effects of psychotropic drugs mentions valproic acid as causing anemia, neutropenia, pure red cell aplasia and thrombocytopenia, and olanzapine as inducing leukocytosis and thrombocytopenia (19). Furthermore, recent evidence associates olanzapine with leukopenia, even recommending that the guidelines for using and monitoring olanzapine be reconsidered (20-22).

The same drug combination could also expose the patients to additive liver damage. Valproic acid may cause serious or even life-threatening damage to the liver that is most likely to occur in the first 6 months after starting treatment (23,24). Olanzapine, in its turn, has also been reported to cause liver injuries of variable severity through different mechanisms (25,26). Nonalcoholic fatty liver disease can also be associated with atypical antipsychotics via the metabolic abnormalities, which they can induce (27). Caution is warranted after starting a psychotropic agent in a patient with hepatic impairment, especially in combination with valproic acid. Use of psychotropic drugs with minimal liver metabolism and monitoring the levels of aminotransferases is considered appropriate in such occasions (28,29). Other ADRs that olanzapine and valproate share are weight gain, somnolence, tremor, dry mouth, and speech disorders (20).

CONCLUSION

A high rate of pDDIs was detected in our patient sample for the period of the hospital stay and less so at discharge. Although it has been found that pDDIs far outnumber those which lead to clinically significant effects, analysis has shown that the real size of the adversely affected patients is nevertheless large enough (30). It is evident that pDDIs lead to ADRs only in the presence of a variety of predisposing risk factors. Given the high incidence of pDDIs, their clinical relevance should not be underestimated. Together with the careful clinical, physio-

logical and biochemical monitoring of the patients, it is essential to consider the pharmacological features of the administered drugs and select those with the least propensity to interact.

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