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Risk of Psychotropic Drug Interactions in Real World Settings: a Pilot Study in Patients with Schizophrenia and Schizoaffective Disorder

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ÖZET:

Günlük klinik pratikte psikotrop ilaç etkileşimleri riski: Şizofreni ve şizoaffektif bozukluğu olan hastalarda bir ön çalışma

Amaç: Psikotik bozukluklarda giderek polifarmasi oranı artmaktadır. Polifarmasi eş zamanlı olarak iki veya daha fazla ilacın birlikte kullanımı olarak tanımlanmaktadır. Psikotrop ilaçların çoğu sitokrom enzim sistemi ile metabolize edildiği için polifarmasi uygulaması ile ilaç-ilaç etkileşim riskinin artacağı öngörülebilir. Bu çalışmada şizofreni ve şizoaffektif bozukluk tanısı konan hastalarda kullandıkları psikotrop ilaçlar arasındaki etkileşim riskinin incelenmesi amaçlanmıştır.

Yöntem: Bu çalışmaya DSM-IV'e göre şizofreni ve şizoaffektif bozukluk tanısı konan, yatarak ya da poliklinikten takip olan, en az 12 haftadır antipsikotik alan 18-65 yaş arası hastalar alınmıştır. En az 4 haftadır eş zamanlı olarak kullanılan antipsikotik ve diğer psikotrop ilaçlar polifarmasi olarak kaydedildi. Etkileşim riskini tespit etmek için, her hastanın kullanmakta olduğu ilaçlar https://drugs.com adresine bireysel tedavi rejimi olarak girildikten sonra profesyonellere yönelik etkileşim bilgilerinden yararlanılarak araştırıldı.

Bulgular: Çalışma grubu şizofreni spektrum bozukluğu (şizofreni, şizoaffektif bozukluk) olan 141 erkek (%58.80), 99 kadın (%41.20) toplam 240 hastadan oluşmaktaydı Tek antipsikotikle tedavi edilen hastaların oranı % 56.6 (s:136), iki veya daha fazla antipsikotik kullananların oranı %43.4 (s:104) idi. Kullanılan ortalama ilaç sayısı 2.58±1.22 (min 1-max 6), ortalama etkileşim sayısı 1.90±2.04 (min 1-max 10) olarak bulundu. Toplam 172 (%71.7) hasta etkileşim riski taşıyan ilaçları kullanmaktaydı, bu hastalarda toplam 417 ilaç etkileşimi riski mevcuttu. Etkileşim riskinin %87.8'i (toplam sayı 366) orta düzeyde idi. Hastaların yaklaşık dörtte biri (sayı 42, %24.4) major, 2 hasta (%1.2) minör ilaç etkileşim riski taşıyan ilaçları kullanmaktaydı. İlaç etkileşimlerinin olası sonuçları arasında ilk üç sırayı antikolinerjik yan etki riski, merkezi sinir sistemi ve solunum depresyonu riski ve QT uzaması riski yer almakta idi.

Sonuç: Araştırmamız şizofreni spektrum bozukluklarında giderek artan çoklu ilaç kullanımı ile birlikte hastaların önemli bir kısmının ilaç-ilaç etkileşim riskiyle karşı karşıya olduğunu, bu etkileşim risklerinden major ilaç etkileşim riskinin büyük çoğunluğunun kardiovasküler riskler, özellikle de QT'de uzama riski olduğuna işaret etmektedir. Bu alanda ileriye dönük daha geniş vaka katılımlı çalışmalara ihtiyaç vardır.

Anahtar sözcükler: şizofreni, şizoafektif bozukluk, psikotrop, polifarmasi, ilaç etkileşimi

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ABSTRACT:

Risk of psychotropic drug interactions in real world settings: a pilot study in patients with schizophrenia and schizoaffective disorder

Objective: The rate of polypharmacy is increasing in patients with psychotic disorders. Polypharmacy is defined as the concomitant use of two or more drugs at a time. As most psychotropic medications are metabolized via the cytochrome enzyme system, it is easy to predict that polypharmacy will increase the risk of drug-drug interactions. This study was planned to evaluate the interaction risks of medications used by patients with a diagnosis of schizophrenia and schizoaffective disorder.

Method: This study enrolled inpatients and outpatients of 18–65 years of age, diagnosed with schizophrenia or schizoaffective disorder according to the DSM-IV classification, who had been receiving antipsychotics for at least 12 weeks. Co-administration of antipsychotic and other psychotropic drugs for at least 4 weeks was recorded as polypharmacy. The risk of interaction was determined as follows: all medications one patient was using were sent to the internet site https://drugs.com as individual treatment regimens, and interaction information for healthcare specialists was used.

Results: The study sample consisted of 240 patients (141 males; 58.8%; 99 females; 41.2%) in total, with the schizophrenia spectrum of diseases (schizophrenia, schizoaffective disorder). One hundred and thirty six (56.6%) patients used only one antipsychotic and 104 (43.4%) patients used 2 or more antipsychotics. The mean number of medications was 2.58±1.22 (min 1-max 6), the mean number of interactions was 1.90±2.04 (min 1-max 10). One hundred and seventy two (71.7%) patients were taking medications with a risk of interaction, with 417 total drug interaction risks. Of the interaction risks, 87.8% (total number 366) were at a moderate level. Approximately one quarter of the patients (n=42, 24.4%) were using medications with a major risk, and two patients (1.2%) were taking drugs with a minor risk of interaction. Among probable outcomes of drug interactions, the first 3 places were occupied by a risk of anticholinergic side effects, a risk of CNS or respiratory depression and a risk of QT prolongation.

Conclusion: The present study reports that an important percentage of patients are exposed to drug–drug interactions with ever-increasing use of multiple medications in the schizophrenia spectrum of diseases, and among these interactions, most major risks were cardiovascular risks, especially QT prolongation. Prospective studies with larger numbers of patients are needed in this area.

Keywords: schizophrenia, schizoaffective disorder, psychotropic, polypharmacy, drug interaction

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INTRODUCTION

Polypharmacy with antipsychotic medications is defined as the simultaneous use of two or more antipsychotic medications[1]. The chronic clinical course of schizophrenia, resistance to treatment, drug side effects, different responses of negative and cognitive symptom clusters to anti-psychotic medications with different receptor profiles may require combination therapy and thus antipsychotic polypharmacy[1-3]. The frequency of antipsychotic polypharmacy in clinical practice has increased after the introduction of atypical antipsychotic medications. Although the frequency of polypharmacy may vary between 46% to 70% in different countries and years, most studies report antipsychotic polypharmacy in nearly half of the patients[5-7]. Anti-psychotic polypharmacy has been reported in 38.2-64.7% of patients with schizophrenia–spectrum diseases in studies done in Turkey[8-12]. Simultaneous use of many different psychotropic medications such as mood stabilizers, antidepressants, benzodiazepines and anti-cholinergics is observed in patients with schizophrenia because of anti-psychotropic polypharmacy, as well as augmentation therapy or treatment of accompanying disorders such as depression or medication side effects[1,2,5,6,13]. The increasing inclination towards polypharmacy has prompted studies investigating this phenomenon in terms of good clinical practice, and benefits and risks for patients[6,14,15]. While some studies report positive effects of polypharmacy on some clinical features such as the duration of hospital stays, and frequency of side effects[5], another claim that there was insufficient evidence that polypharmacy might constitute a more effective treatment option. It has also been reported that this may compromise compliance, and may increase the frequency of side effects and mortality due to pharmacokinetic and pharmacodynamic drug interactions[15-19]. The progressive increase of polypharmacy in psychotic disorders increases the probability of harmful effects of drug–drug interactions. Pharmacodynamic interactions have synergic or antagonistic effects on a medication's effects on target receptors, and pharmacokinetic interactions result from interactions involving the absorption, metabolism, excretion or distribution of a medication. As most psychotropic medications are metabolized by the cytochrome (CYP) enzyme system, it may be predicted that the risk of drug–drug interactions will increase as a result of polypharmacy[15]. Most studies have focused on the clinical effects of drug interactions between antipsychotics. There are few studies systematically defining the drug interactions that patients might encounter in daily clinical practice. Guo et al.[20] have reviewed the medical records of health insurance system, and detected potentially dangerous drug interactions in approximately 23% of patients taking antipsychotic medications. Although the frequency of polypharmacy among patients with schizophrenia is as high as in other regions of the world, no study has been undertaken to investigate the risk of drug interactions that these patients may experience in Turkey. We hope that this study of the risk of interaction between psychotropic medications of patients diagnosed as having schizophrenia and schizoaffective disorder may contribute to an awareness of the negative outcomes of polypharmacy in daily clinical practice.

METHODS

The baseline data on pharmacotherapy of a prospective naturalistic study (Project Number: 2008TPF029) was supported by the Committee of Scientific Research Projects of Pamukkale University, in which the association between antipsychotic medication intake and metabolic syndrome in patients with schizophrenia spectrum of disorders was planned to be investigated[21]. Inpatients and outpatients diagnosed with schizophrenia or schizoaffective disorder according to the DSM-IV classification, aged 18-65 years, who had been receiving antipsychotics for at least 12 weeks were included in this study. The Medical Ethics Committee of Pamukkale University approved the study protocol (protocol no: 4837,

21.10.2008). The objectives and procedures of this study were explained to all patients; they were informed that their ongoing treatments would not be affected by study procedures prior to initiation of the study, and written informed consent was also obtained from all subjects.

The patients were recruited from two treatment settings (Pamukkale University, Psychotic Disorder Outpatient Clinics and Denizli State Hospital). Patients with the following exclusion criteria were not recruited: psychotic disorder or mood disorder due to a general medical condition, dementia or substance abuse. Two hundred and forty patients who gave informed consent were enrolled into study.

Antipsychotic medications and other psychotropic medications that had been taken simultaneously for at least 4 weeks were recorded as polypharmacy. The internet site drugs.com was used in determining the interaction risk. This site is an organization which reports its aim as being the largest independent source of information for health professionals on drugs and related health information in the internet[22]. The drugs each patients was being given were entered at the "drugs.com" site as an individual treatment regimen and searched for drug interactions, requesting information for professionals. In patients who were taking medications that were not in this site's list (such as zuclopenthixol, flupentixol, amisulpride) in two-drug combinations, the drug interaction status was recorded as "unknown". In combinations containing three drugs, interaction information on the other drugs were recorded. This site classifies the significance of drug interaction risks in three categories as "minor", "moderate" or "major". There are precautions of "generally avoid", "close monitorization", or "contraindicated" under the "major interaction risk" headline. Major interaction risk is highly clinically significant; combinations should be avoided as the risk of the interaction outweighs any benefit. A moderate interaction is clinically significant. Combinations should usually be avoided or used only under special circumstances. A minor interaction is minimally clinically significant. Risk should be assessed and minimized by considering an alternative drug. Steps should be taken to circumvent the interaction risk and/or a monitoring plan should be instituted. The probable outcomes of the drug interaction and the interaction mechanisms (blood level changes of drugs due to CYP enzyme induction and increase in QT interval) from the professional interaction information were also recorded.

The statistical analysis was done with SPSS 17.0 (for Windows) software. Descriptive statistics were presented as frequency, percentage, mean, standard deviation, minimum and maximum values. The linear association between variables was investigated with Pearson correlation analysis. The Mann-Whitney U test was used to compare continuous variables. The significance level was considered as $p \leq 0.05$.

RESULTS

The study sample consisted of 141 male (58.8%) and 99 female (41.2%) patients (240 patients in total) with a schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder). The mean age of the patients was 38.25±11.98 years, mean duration of education was 8.13±4.0 years, and mean duration of illness was 12.4±9.32 years. The mean age of onset was 25.63±8.33 years; mean number of hospitalizations was 2.59±3.27. Follow ups were conducted for 74.1% (181 patients) a university hospital and 24.6% (59 patients) at a state hospital.

One hundred and thirty-six (56.6%) patients used only one antipsychotic and 104 (43.4%) patients used 2 or more antipsychotics. The most frequently used monotherapy consisted of an atypical antipsychotic medication (121 patients, 50.4%); 62 patients (25.8%) used a combination of two or more atypical antipsychotics. The most frequently used antipsychotic drug was risperidone (37.5%), which was followed by olanzapine (21.3%). The antipsychotic medications that the patients used are presented in Table 1.

Mood stabilizers were used by 26.6% of the patients. The most frequently used mood stabilizer was valproate/valproic acid (VAL) (15.8%, 38 patients), which was followed by lithium (5%; 12

Table 1: Antipsychotics used by the patients

	n	%
Atypical antipsychotic monotherapy	121	50.40
Typical antipsychotic monotherapy	15	6.3
Typical+typical	1	0.4
Atypical+typical	41	17.1
2 or more atypical antipsychotics	62	25.80
Total	240	100
Antipsychotics		
Risperidone	90	37.5
Olanzapine	51	21.3
Quetiapine	50	20.80
Amisulpride	38	15.8
Aripiprazole	23	9.6
Zuclopenthixol	22	9.2
Flupentixol	18	7.6
Ziprasidone (ZIP)	16	6.7
Chlorpromazine	14	5.8
Clozapine	12	5
Paliperidone	10	4.2
Fluphenazine	8	3.2
Haloperidol	7	2.9
Pimozide	4	1.7

Table 2: The Numerical distribution of drug couples with a risk of interaction

Number of drug couples	Number of patients with interaction risk	%
1	90	52.2
2	4	2.3
3	43	25.0
4	7	4.1
5	10	5.8
6	9	5.3
7-10	9	5.3
Total	172	100

patients), carbamazepine (CBZ) (2.9%; 7 patients) and lamotrigine (2.9%; 7 patients). Forty-two patients (17.5%) were taking antidepressants, the most frequently used of which was venlafaxine (5%; 12 patients) followed by sertraline (3.8%; 9 patients), and citalopram/ escitalopram (3.8%, 9 patients). Three patients (1.3%) were taking fluoxetine, tricyclic antidepressants (TCA), and one patient (0.4%) was taking fluvoxamine, paroxetine, mirtazapine and milnacipran. Anticholinergics were given to 96 patients (40%), and benzodiazepines to 18 patients (7.5%). Eight patients (3.3%) were given propranolol.

The mean number of medications used was 2.58±1.22 (min 1-max 6) and the mean number of interactions was 1.90±2.04 (min 1-max 10). one hundred and seventy-two patients (71.7%) were taking medications, which had an interaction risk. There were 417 drug interaction risks, in total. Of the 172 patients with a risk of drug interaction, approximately half (52.2%) were taking one pair of drugs with an interaction risk, a quarter (25%) were taking 3 pairs of drugs with an interaction risk. Only in 1/5 of the patients (48 patients; 20%) no risks of drug interaction could be detected. Information on drug interaction risk could not be found in 21 patients (8.8%). The numerical distribution of drug pairs carrying an interaction risk is presented in Table 2.

The most frequent interaction risk level was the moderate risk of interaction (total number 366; 87.8%). Approximately one in four patients (42 patients; 24.4%) were taking drugs with a major risk of interaction, and 2 patients (1.2%) were taking drugs with a minor risk of interaction. Major drug interaction risks constituted 11.8% of all drug interactions. The majority of major drug interaction risks consisted of prolongation of the QT interval (83.3%), risk of hypotension–serious bradycardia (9.5%) and drug interactions causing changes in blood drug levels (7.2%). Moderate risks of drug interaction consisted of anticholinergic side effects (43.9%) and CNS and respiratory depression (27.9%). The probable outcomes of drug interactions, in descending order, were risk of anticholinergic side effects, CNS and respiratory depression and QT interval prolongation. The risk of an increase in anticholinergic side effects constituted 38.6% of all drug interactions, which was followed by an increase in the risk of CNS and respiratory depression in 24.5% of patients. The prolongation of the QT interval (14.6%), change in blood drug levels (11.9%) and extrapyramidal side effects (EPS) and central nervous system toxicity (3.8%) were other risk factors respectively. All of the risks of minor drug interaction were related to changes in blood drug levels. The level and probable outcomes of drug interaction risks that the patients could experience are summarized in Table 3.

The probable outcomes of drug interactions and

Table 3: The levels and probable outcomes of drug interaction risks of the patients that were observed

Interaction risk level	Major*		Moderate*		Minor*	
Possible interaction outcome	**Patient number (%)**	**Interaction number (%)**	**Patient number (%)**	**Interaction number (%)**	**Patient number (%)**	**Interaction number (%)**
QT prolongation	35 (83.3)	42 (85.7)	17 (6.7)	19 (5.2)	-	-
Change in drug blood level	3 (7.2)	3 (6.2)	42 (16.3)	45 (12.3)	2(100)	2 (100)
EPS**/neurotoxicity		-	15 (5.9)	16 (4.3)	-	-
CNS – resp.depression***		-	59 (23.1)	102 (27.9)	-	-
Anticholinergic side effect		-	100 (39.1)	161 (43.9)	-	-
Hepatotoxicity		-	9 (3.5)	9 (2.5)	-	-
Hypotension-serious bradycardia	4 (9.5)	4 (8.1)	9 (3.5)	9 (2.5)	-	-
Teratogenic risk		-	5 (1.9)	5 (1.5)	-	-
Total	42 (100)	49 (11.8)	256 (100)a	366(87.8)	2 (0.4)	2(100)

Possible interaction outcome	Total Patient number (%)	Total Interaction number (%)
QT prolongation	61 (14.6)	
Change in drug blood level	50 (11.9)	
EPS**/neurotoxicity	16 (3.8)	
CNS – resp.depression***	102 (24.5)	
Anticholinergic side effect	161 (38.6)	
Hepatotoxicity	9 (2.3)	
Hypotension-serious bradycardia	13 (3.1)	
Teratogenic risk	5 (1.2)	
Total	417 (100)	

*: percentage of the column, **: extrapyramidal side effects, ***: central nervous system and respiratory depression, especially in the elderly and the debilitated patients,
[a]: As one patient may have more than one moderate drug interaction risks, the total number is more than the 172 patients with drug exposure

Table 4: Distribution of interaction risks according to drugs, probable mechanisms and outcomes

Outcome of interaction risk	Interacting drugs
QT prolongation *Major level (n: 42)*	12 (28.5%)citalopram with quetiapine /fluphenazine/ paliperidone /risperidone /pimozide /haloperidol 10 (23.8%) ziprasidone with risperidone /quetiapine/ pimozide/ chlorpromazine 9 (21.4%) quetiapine with lithium/ fluphenazine/ haloperidol/ pimozide 8 (19%) clozapine with risperidone/ quetiapine/ haloperidol /aripiprazole /fluphenazine 3 (7.1%) haloperidol with lithium/ chlorpromazine/ fluphenazine ***Explanation:*** 11 (26.2%) Contraindicated interaction (10 interactions with ziprasidone,1 quetiapine-pimozide interaction)
Moderate level (n:19)	19 (100%) quetiapine with risperidone /fluoxetine/ chlorpromazine interaction
Drug level change *Major level (n:3)*	3 (100%) quetiapine-CBZ* interaction ***Explanation:*** Decrease in quetiapine level with CBZ CYP**450 induction
Moderate level (n: 45)	Total 20 (44.4%) VAL*** interaction 18 (90%) VAL–risperidone, 2(%10) VAL-TCA**** interaction ***Explanation:*** Risperidone by causing VAL to detach from the serum proteins, and TCA inhibiting CYP 450 system, cause an increase in VAL levels
	7 (15.6%) CBZ with risperidone/aripiprazole/fluoxetine/ ***Explanation:*** CBZ decreases risperidone and aripiprazole levels by CYP induction Fluoxetine may change CBZ level by CYP inhibition
	12 (26.7%) sertraline/paroxetine/fluoxetine/citalopram/escitalopram with risperidone/aripiprazole/clozapine interaction ***Explanation:*** These antidepressants my increase levels of risperidone, aripiprazole, clozapine by CYP 2D6, 1A2 inhibition
	6 (13.4%) lamotrigine and clozapine/ olanzapine/ risperidone interaction ***Explanation:*** Lamotrigine may increase clozapine and risperidone blood levels, olanzapine may cause a decrease in lamotrigine levels, by unknown mechanisms
Minor level (n:2)	2 CBZ-citalopram/ziprasidone ***Explanation:*** ZIP level increase by CYP induction, increase in CBZ levels by CYP inhibition
Hepatotoxicity (n: 9)	All olanzapine and VAL interaction ***Explanation:*** All at a moderate level
Bradycardia-hypotension *Major level (n:14)*	All interactions between benzodiazepines and olanzapine or clozapine ***Explanation:*** mechanism not clearly known
Moderate level (n:9)	All propranolol and biperidene/ quetiapine/ lithium or olanzapine interaction ***Explanation:*** Probable mechanism peripheral alpha-1 adrenergic blockage
EPS neurotoxicity risk *(n:16)*	13 (81.3%) lithium with risperidone /olanzapine /aripiprazole/ ziprasidone interaction 3 (18.7%) haloperidol-olanzapine interaction ***Explanation:*** All moderate level interactions

*carbamezapine, **cytochrome, ***tricyclic antidepressants, ****valproic acid/Na valproate

distribution according to medications are summarized in Table 4. These were analyzed according to frequency, in descending order, as follows:

Increase in anticholinergic side effects: This was the most common (38.6%) risk of drug interaction and all were at a moderate level. Most originated from the interaction of biperidene with antipsychotics with anticholinergic characteristics (risperidone, quetiapine, olanzapine, chlorpromazine, aripiprazole, haloperidol, clozapine) (74.5% n=120). The rest were due to an interaction between antipsychotics with anticholinergic properties.

Central Nervous System (CNS) and respiratory depression: This was the second most common (24.5%) risk of drug interaction, again all at a moderate level. The warning in "drugs.com" for this interaction included caution for use of multiple medications which had an effect on the CNS, in especially old and debilitated patients. Of a total of 120 risks of interaction related to the central nervous system (CNS) and respiratory depression, about 40% (n=44, 36.7%) originated from the interaction between VAL and different medications such as quetiapine ,biperidene and antidepressants. The rest were due to interactions between multiple psychotropic medications. For example, there were five different drug interaction warnings for a patient taking VAL, quetiapine, aripiprazole and venlafaxine for CNS and respiratory depression (all interactions except the one between quetiapine-aripiprazole). Only two of the patients (3.6%) that were exposed to this interaction were older than 60 years.

QT prolongation: Sixty-one interactions were detected, which carried a risk of QT prolongation. Forty two (68.9%) of these were major interaction risks, and 11 (26.2%) had a warning of contraindication. Those interactions that had an alert for contraindication were between ziprasidone and various antipsychotics. Of the 42 major drug interaction risks, 28.5% were the interaction of citalopram or escitalopram with different antipsychotics, 21.4% were the interaction of quetiapine with lithium and typical antipsychotics and 19% were the interaction of clozapine with typical and atypical antipsychotics. Of 19 moderate interactions with a risk of QT prolongation, all originated from an interaction between quetiapine with risperidone (n=17), chlorpromazine (n=1) or fluoxetine (n=1). The clusters of medications with a significant risk of QT prolongation were ziprasidone, quetiapine, citalopram/escitalopram, clozapine and haloperidol.

Other cardiovascular risks: These constitute 3.1% of all interaction risks (n=13), and 9.5% of all major drug interaction risks. Of this group, 30.8% (n=4) were at major risk of interaction between clozapine and benzodiazepines for cardiac and respiratory arrest, cardiovascular collapse and sudden death. The rest were at risk of orthostatic hypotension originating from an interaction between propranolol and clozapine, risperidone and quetiapine.

Change in blood drug level: In 34 of 40 patients (85%) exposed to an interaction risk that could cause a change in blood drug level, there was a risk of change in blood levels of 2 drugs in 4 patients (10%) and 3 drugs in 2 patients (5%). All of the major drug interaction risks that were related to drug blood levels were due to a quetiapine–CBZ interaction. In approximately half (44.4%, n=20) of the 45 moderate interaction risks that constituted this group, interaction of VAL with different medications, and in a quarter (n=11, 24.4%) interaction of CBZ with different drugs played a role. The most frequent interaction with VAL was with risperidone (n=18, 90%). Of this group, 15.6% included a change in the blood level of antipsychotics (risperidone, aripiprazole) due to CYP induction by CBZ. The interaction risk in which sertraline, fluoxetine, paroxetine or citalopram /escitalopram, which inhibit CYP, could cause an increase in the blood levels of antipsychotics (such as clozapine, risperidone, aripiprazole) that are metabolized by this system, was detected in 26.7% of this group. The

interaction of lamotrigine with olanzapine, clozapine and risperidone was found to constitute 13.4% of this group.

EPS-neurotoxicity risk: Of the 16 risks of this interaction, all were moderate; 81.3% (n=13) consisted of the interaction between lithium and risperidone, olanzapine, aripiprazole, or ziprasidone and 18.7% (n=3) consisted of the interaction between haloperidol and olanzapine.

Hepatotoxicity: Liver toxicity constituted nine (2.3%) of all the interaction risks and was a moderate risk originating from olanzapine interacting with. VAL.

Teratogenic risk: All of 5 interaction risks were moderate risks, which originated from the interaction between VAL and benzodiazepine. Only two of the patients carrying this risk were between ages 20-39.

The Relationship between Drug Interaction Risk and Demographic and Clinical Variables

A strong positive correlation was detected between the number of medications taken and risk of interaction (r=0.824, p=0.001). There was no statistically significant difference in the number of psychotropic medications used between genders. However, there was a significant weakly negative correlation between the age at which the disease occurred and the number of medications used and risk of drug interactions (r=-0,156 p=0.016; r=-0.174 p=0.010, respectively). A weakly significant positive correlation was found between the number of hospitalizations and risk of drug interaction (r=0.207, p=0.002).

DISCUSSION

This is a naturalistic study, investigating the frequency of polypharmacy in daily clinical practice and the probable risk of psychotropic drug interactions in patients with schizophrenia and schizoaffective disorder. We detected use of two antipsychotic medications by third (35.8%) of the patients, use of medications carrying risk of interaction by more than two thirds (71.7%), and use of medications with a major risk of interaction by approximately one quarter of the patients. A majority of the major drug interaction risks (83.3%) consisted of QT prolongation, which was followed by risks of serious hypotension, bradycardia, and probable changes in blood drug levels.

Although antipsychotic polypharmacy is not recommended by treatment guidelines for the treatment of schizophrenia spectrum of diseases, it is quite frequent in daily practice. In a study investigating use of multiple antipsychotic medications in 147 studies including 1,418,163 participants, the rate of antipsychotic polypharmacy was found to be 16% in North America, 23% in Europe and 32% in Asia, with a mean rate of 19.5%[22]. Use of multiple antipsychotic medications was detected in 46.2% of patients in a large sample of 16,083 Finnish patients with schizophrenia[6]. We detected antipsychotic polypharmacy in 46.3% of our patients, with two drugs being used in more than two thirds (35.8%) and with more than 2 drugs in 7.5%. The rate of antipsychotic polypharmacy has been reported to be 38.2% in a Turkish study (2002) conducted in hospitalized patients with the schizophrenia spectrum of diseases[8], and has been reported as 49%-54.4% in following other studies[10,11]. Our findings support the idea that polypharmacy is a prevalent and increasing practice in schizophrenia spectrum diseases, in accordance with the data in the current literature. Antipsychotic polypharmacy has been found to be associated with factors reflecting the chronicity of schizophrenia and resistance to treatment, such as disease severity, duration of illness, and duration of hospital stay[5,6,13,23]. We found a negative correlation between the number of medications used and age of onset of disease, and a positive correlation between the number of hospitalizations and the risk of drug interactions. An early onset of disease and multiple hospitalizations are conditions which reflect a poor prognosis and resistance to treatment, which also increased the risk of polypharmacy. The second most frequently used medications in schizophrenia

spectrum diseases after antipsychotics are the mood stabilizers, with VAL being the most frequently used among these[5,24]. We also found the mood stabilizers to be the second most frequently (26.6%) used class of psychotropic medications after antipsychotics. In clinical studies, antidepressants were reported to be prescribed in 11%-43% of the patients for accompanying depression and negative symptoms in schizophrenia spectrum diseases[25-27]. We found the frequency of antidepressant use to be 17.5% in our study, among which venlafaxine was the most commonly utilized drug, followed by sertraline and citalopram / escitalopram. We found that anticholinergics (40%) and benzodiazepines (7.5%) were the most commonly used medications for the treatment of drug side effects. Anticholinergics are frequently used for the treatment or prevention of extra-pyramidal symptoms[25]. The mean number of medications per patient was found to be 2.58. We detected the use of one couple of medications carrying an interaction risk in 52.2% of the patients, use of 3 couples of medications in 25% of patients, with a significant association between early onset, hospital stays and number of drugs used with the risk of interactions. In summary, it may be suggested that the increasing use of polypharmacy in schizophrenia spectrum diseases with antipsychotics and non-antipsychotic psychotropic medications might increase the risk of drug interactions, thus increasing morbidity and mortality rates, along with healthcare service costs. Guo et al. investigated the moderate and serious drug–drug interaction risk in 27,909 patients with schizophrenia, based on prescription billing, and detected a serious risk of drug interactions in a quarter of patients using antipsychotic medications. Risperidone, olanzapine, quetiapine and clozapine occupy the first four places among all interactions[20]. We also found a major risk of drug interactions in 24.4% of the patients. A vast majority of these interactions were the risk of QT prolongation, and 11 (26.2%) had a warning of contraindication. The warning of contraindication was related to ziprasidone and antipsychotics such as chlorpromazine, pimozide, quetiapine and risperidone. Another risk of major drug interaction was with the use of citalopram /escitalopram, clozapine and quetiapine, with typical antipsychotics such as haloperidol, fluphenazine, chlorpromazine, as well as the interaction between lithium and quetiapine which could result in QT prolongation.

Ziprasidone is the best-known antipsychotic medication, which is associated with QT prolongation among atypical antipsychotics[28]. In particular, the intravenous use of haloperidol, pimozide and chlorpromazine was found to be associated with QT prolongation among typical antipsychotics[28-32]. QT prolongation, which is one of the most prevalent cardiac side effects of antipsychotics, is known to create a tendency for the development of a fatal arrhythmia (torsades des pointes; TdP)[33]. Sudden unexpected deaths are 2 times more prevalent than the normal population among patients with schizophrenia who use antipsychotic medications[29].

Amisulpride, chlorpromazine, clozapine, cyamemazine, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone were categorized in group A (strong warning against torsadogenic risk) in a new pharmaco-vigilance study investigating the torsadogenic risks of antipsychotics in European countries. The first four places in terms of cases of torsades des pointes are occupied by ziprasidone, haloperidol, risperidone and quetiapine according to the adverse effect reports of the FDA[34]. QT prolongation due to haloperidol, sertindole, clotiapine, phenothiazines, fluoxetine, citalopram (including escitalopram), and methadone were frequently reported in a new study investigating QT prolongation in psychiatric patients due to medications[35]. The risk of QT prolongation was reported to increase with use of co-administration of antipsychotics with antidepressants and lithium[36-39]. Citalopram has an FDA warning for dose-dependent QT prolongation among antidepressants[38,39], whereas escitalopram has less effect on the QT interval[28]. The drug interactions where the risk of QT prolongation was most likely involved ziprasidone, quetiapine, citalopram/ escitalopram, clozapine, and haloperidol in our

study, in accordance with this data. These medications, except quetiapine, were used by a small group among our patients (ziprasidone 6.7%, clozapine 5%, and citalopram-escitalopram 3.8%, Table 1). The fact that 75% of the major drug interaction risks causing a QT prolongation originated from co-administration of ziprasidone, clozapine and citalopram–escitalopram with psychotropic medications, means that these drugs were frequently used with other psychotropic agents that had a negative effect on the QT interval. Co-administration of medications that disrupt cardiac depolarization increases the risk[30,40]. In the present study, most of the moderate interaction risk resulting in QT prolongation was caused by quetiapine–risperidone. Although quetiapine was reported to cause a low risk, and risperidone moderate risk of QT prolongation, both were reported in cases of torsades des pointes[28,34]. Considering this may be beneficial, when using these medications, which are frequently co-administered in daily clinical practice[41].

Among the cardiovascular risks in our study, one third of the hypotension–serious bradycardia risk was a major drug interaction risk, which originated from the clozapine–benzodiazepine interaction. The rest was caused by an interaction between propranolol and biperidene, quetiapine, lithium or olanzapine, which constituted a moderate risk. Although its mechanism is not completely known and a causality relationship cannot be shown, intravenous benzodiazepine and clozapine have been reported to have an additive effect on the cardiovascular and respiratory system, and cases of hypotension, collapse, cardiac and respiratory arrest and sudden death have been reported in their co-administration[42,43]. Consideration of this risk of a clozapine–benzodiazepine combination, which we could detect in a relatively low frequency among all drug interaction risks, may be beneficial due to the fatal consequences.

Due to the possibility of serious and fatal complications such as orthostatic hypotension, syncope, transient ischemic attack, stroke or myocardial infarction (MI), resulting from the alpha 1 adrenergic receptor blockage of psychotropic medications, this is another cardiovascular side effect[16,26]. We did not observe a major drug interaction risk concerning this condition, although there is a moderate interaction risk associated with beta blockers and psychotropic medications such as clozapine, risperidone and quetiapine which may cause adrenergic blockage and show more frequent orthostatic hypotension side effects.

In summary, our findings underline the need for increasing awareness of the cardiac side effects of psychotropic drugs, and the importance of prior evaluation of risk and monitoring for changes in the QT interval. The internet site that we used gives a warning of contraindication for the combination of ziprasidone with many antipsychotics. As far as we know, there is no source of information in Turkey, providing national information on drug interactions to healthcare professionals and patients. In view of the progressive globalization of knowledge, it may easily be predicted that we may experience lawsuits for malpractice related to drug interactions in the near future. For this reason, developing a recording and warning system for serious drug interactions for healthcare providers should be considered as a priority.

Evaluation of pharmacokinetic interactions of antipsychotic drugs should take into consideration the substrate, inhibitor, and inducer properties for the CYP P450 isoenzymes of all combined drugs. All antipsychotic drugs are metabolized via the hepatic CYP450 enzyme system, especially via CYP1A2, CYP2D6 and CYP3A4[15]. The administration of one antipsychotic with another antipsychotic or with another drug may competitively inhibit or induce this enzyme system. The plasma levels of affected antipsychotics increase because of this and adverse effects also increase[15,44]. The risk of a change in blood drug level constituted 11.9% of all risks of interaction in the present study, three (7.2%) of which were major drug interaction risks and all interactions of quetiapine-CBZ. CBZ speeds up the degradation and elimination of quetiapine by inducing CYP3A4, and the blood level of quetiapine shows a considerable decrease[45]. We detected a moderate interaction risk of 7.5% that CBZ may decrease the blood levels of aripiprazole and

risperidone by a similar mechanism[45,46].

These blood level changes are important clinically, as they mean a loss or decrease in efficacy. Among other moderate interaction risks that may cause a change in blood drug levels, the interaction between VAL and risperidone was detected in 44.4%. The risk of interaction between CYP-inhibiting antidepressants and antipsychotics that are degraded by these enzymes that may cause an increase in blood levels of antipsychotics was detected in 26.7%. The most frequent interaction with VAL was observed with risperidone. Risperidone causes detachment of VAL from serum proteins, thus causing a change in blood levels[46,47]. An interaction risk of 26.7% was observed that can cause an increase in the blood levels of antipsychotics that are degraded with this enzyme, between CYP inhibiting antidepressants (sertraline, paroxetine, fluoxetine, citalopram-escitalopram) and antipsychotics (risperidone, aripiprazole, clozapine). These antidepressants may increase the levels of risperidone, aripiprazole or clozapine by CYP 2D6, 1A2 inhibition[27,44]. The interaction of lamotrigine with olanzapine, clozapine and risperidone was among the other blood drug level interaction risks. There are reports of lamotrigine changing the blood levels of risperidone and quetiapine. The probable mechanism may be glucuronidation[48-50].

Guo et al. have reported the risk of interaction of risperidone with CYP 2D6 inhibiting antidepressants[20]. Our findings suggest that the risk of interaction with blood drug levels may reach a moderate level in approximately 1/10 patients, and this risk should be taken into consideration in the evaluation of patients with schizophrenia, when mood stabilizers and antidepressants are added to treatment.

In the present study, most frequently an increase in anticholinergic side effects and the risk of CNS and respiratory depression in elderly and debilitated patients were detected as moderate level interaction risks. Most of the anticholinergic side effect risk was related to use of biperidene. The use of anticholinergics for EPS thought to have a negative effect on the cognitive symptoms in patients with schizophrenia[51]. This frequent application of daily clinical practice may be important in peripheral anticholinergic effects as well as cognitive symptoms. Of the patients taking medications with a risk of CNS and respiratory depression among elderly and debilitated patients, only 3.6% were over 60 years, so that this risk may be considered rare in clinical practice. All of the EPS–neurotoxicity risk that was detected in the present study was of a moderate level, constituting 4.3% of all interactions. Most were related to the interaction of lithium with risperidone, olanzapine, aripiprazole, and ziprasidone, while some were related to the interaction of haloperidol and olanzapine. Use of olanzapine–haloperidol was observed in only 3 patients in the present study, whereas this was reported by Guo et al.[20] as the drug couple with the most frequent risk of interaction. As the therapeutic window of lithium is rather narrow, combination with an antipsychotic increases the risk of neurotoxicity[52]. At least half of the patients taking lithium have been reported to use an additional antipsychotic medication in a review[53]. Clinical observations have reported an increase in the risk of permanent neurotoxicity of lithium when used in combination with agents that cause dopaminergic blockage, and this may occur as serious dyskinesia of the body and orofacial structures[52]. Although EPS risk is decreased by the frequent use of the second generation of antipsychotics, use of the second-generation antipsychotics with lithium in particular seems to increase neurotoxicity, and this in turn increases symptoms like dyskinesia. Care would be prudent in the use of such combinations. In the present study, the rarest moderate level interaction risks were liver toxicity (2.5%) and teratogenic risk (1.5%). The common drug for both interaction risks were VAL. The hepatic toxicity was related to the olanzapine-VAL couple, while the teratogenic risk was related to the VAL-benzodiazepine couple. In patients with fatal hepatic toxicity due to VAL, 32.4% were found to use monotherapy, 67.6% were using multiple medications; additional medications with VAL were reported to increase both the frequency and

severity of hepatic toxicity[54]. The mechanism of hepatotoxicity due to olanzapine is not clearly known. It has been suggested to be dose–related, metabolic idiosyncratic, hypersensitivity or may be related to the CYP enzyme system[55-58]. The co-administration of VAL with medications with a risk of hepatic toxicity may be considered as a rare interaction with serious consequences. VAL is a drug with known teratogenic risks[59,60]; and its combination with benzodiazepines seems to increase the risk[61,62]. For this reason, it is important that female patients with a potential for pregnancy should be informed and closely monitored.

In conclusion, although the results of this study may not be generalized to the whole population, our findings suggest that a significant portion of patients with a schizophrenia spectrum diseases will be exposed to risk of drug–drug interactions with progressively increasing polypharmacy, and most of the major drug interaction risks are those causing cardiovascular risks, particularly QT prolongation. They also suggest that the risk of probable drug interactions that could affect the drug blood level should be considered in patients in whom mood stabilizers or antidepressants are added to the treatment. This recalls the need for a system of early warning for drug interactions that can be used in practice, in outpatient clinics, which may decrease the risk of mortality and morbidity that may accompany these incidents. There are a limited number of studies in the medical literature on drug–drug interactions in schizophrenia spectrum diseases, and these are based on retrospective inspection of general medical records[63]. As far as we know, no study has been done to evaluate the drug–drug interactions that patients with schizophrenia spectrum diseases experience in daily clinical practice, in real life conditions. Our study is important as a preliminary study evaluating the risk of drug–drug interaction individually in this area for each patient. Limitations include the low number of patients included in this study, evaluation of only the risk of interaction between psychotropic medications, cross-sectional assessment, absence of information on some medications (especially European medications) in the source ("drugs.com") used to determine the interaction risk and lack of use of more professional software for the analysis. Prospective studies with larger numbers of patients are needed in this area.

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