EVALUATION OF POTENTIALLY INAPPROPRIATE PSYCHOTROPIC USE IN ELDERLY PSYCHIATRIC PATIENTS

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ABSTRACT

Introduction: Prescription of potentially inappropriate medications is common in older adults with high medical comorbidity and are at great risk for adverse drug reactions. The objective of this study was to evaluate the potentially inappropriate psychotropics prescribing among geriatric patients with a psychiatric disorder.

Materials and Method: This was a cross-sectional study of geriatric patients older than ≥65-year-old attended a psychiatry outpatient clinic. The socio-demographic data, the psychiatric diagnosis of the patients, the number and sort of potentially inappropriate psychotropics as defined by Beers Criteria 2019 were recorded.

Results: In total 235 patients with a mean± standard deviation age of 73.95 ± 7.30 years were included the study. The mean number of psychotropics and total drugs were 1.80±0.88 and 5.14±1.90, respectively. The rate of potentially inappropriate psychotropics was 35.7% and the most commonly prescribed psychotropics were antipsychotics (52.4%). Drug-drug interactions were found in 20.9% of patients. Female gender, the number of psychotropics, and total drugs used were significantly higher in potentially inappropriate psychotropics users than non-users. In logistic regression analysis, the use of potentially inappropriate psychotropics was associated with the number of psychiatric medications (OR=3.619, 95%CI 2.157-6.072; p<0.01) and the number of total drugs (OR=1.197, 95%CI 0.997-1.438; p=0.044).

Conclusion: The prevalance of potentially inappropriate psychotropics use is high in elderly psychiatric patients. The most important determinants of potentially inappropriate psychotropics use were the number of medications and psychotropics being taken. Rational prescribing of psychotropic drugs in the elderly is a key component to reduce adverse drug events and drug-drug interactions.

Key Words: Potentially Inappropriate Medication List; Aged; Psychotropic Drug.

INTRODUCTION

The elderly population is increasing at a high rate and in Turkey, the proportion of the elderly people in the total population was determined as 9.1% in 2019 (1). This group with high chronic conditions and comorbid medical diseases stands out in the use of multiple medications. Besides this, age-related physiological changes in liver functions, renal clearance, and serum protein levels alter pharmacokinetics and pharmacodynamics (2). Therefore, the geriatric population has a risk of developing adverse drug reactions (ADRs) and drug-drug interactions (3).

Potentially inappropriate medications (PIMs) in the elderly are described as drugs whose adverse effects for this population are outweighed their gain and/or the evidence about their benefits is insufficient, when a safer alternative is available (4). PIMs use was shown to be associated with more ADRs, emergency service admissions, hospitalization, and lower quality of life (5, 6). It was stated in previous studies that PIMs intake was almost two-fold higher in geriatric patients with a psychiatric disorder than other geriatric patients (7).

Most of the PIMs use in the elderly population consist of psychotropic drugs (7, 8). Thus, potentially inappropriate psychotropics (PIPs) use is an important concern in this group. It was reported that the prevalence of PIPs use among elderly is about 30%. Additionally almost half the patients who use psychotropic agents recieved at least one PIPs (9). It has been shown that psychotropics constituted the majority of the drugs responsible for ADRs in older patients admitted to the emergency department (10). PIPs use in the elderly is reported to be associated with falls, fractures, cognitive decline, and hospitalization (11).

Different tools have been developed to evaluate PIMs use. One of the most commonly used ones is Beers Criteria which was developed by the American Geriatrics Society (AGS) (12). The criteria were lastly updated in 2019 based on the most recent literature to serve as a tool for evaluating effective, safe, and appropriate treatment regimens in older adults.

The main objective of this study was to evaluate the prevalence and sort of the PIPs prescription according to Beers Criteria 2019 among the psychiatric outpatients aged ≥65 years. Another objective was to determine the drug-drug interactions and risk factors related to PIPs use in the elderly.

METHODS

Patients

This research was a prospective, cross-sectional and single-centered study that comprises the patients 65 years of age and older who were admitted to outpatient clinics of Bolu Abant Izzet Baysal Mental Health Research and Training Hospital between June and December 2019. The individuals who used any psychotropic medication for at least 4 weeks and accepted to participate in the study were included. The written informed consent was obtained from all participants prior to study participation. If the patient's clinical or cognitive status did not permit the signing of the informed consent, the psychiatrist referred to the person responsible for decisions concerning the patient. The patients who were under 65 years of age, reject to participate in the study or had a lack of data about their medication history were excluded from the study.

The psychiatric diagnosis of the patients was made according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria by the psychiatrists working in the psychiatry outpatient clinic of the hospital. The socio-demographic data, the history of chronic medical diseases, and all the medications used by the patients were collected with a form prepared by the researchers. The information about medications that the patient used was also checked from the electronic National Personal Health System (e-nabiz) of each patient.

The medical ethics committee of Bolu Abant Izzet Baysal University approved the study (no:235

date:22.05.2019). The study was compiled with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration.

Identification of PIPs

The total number of drugs prescribed per day and used at least 4 weeks were recorded, excluding topical and inhaled medications, vitamins, dietary supplements, and medical devices.

PIPs and inappropriate drug-drug interactions were identified using the 2019 updated version of AGS Beers Criteria for older adults. PIPs are listed as accompanying the moderate-high level of evidence and the strong strength of recommendation. The chronic psychotropic medication use was evaluated in two sections according to this guideline: (1) 'potentially inappropriate medications used in older adults (Beers Table 2)' and (2) 'potentially clinically important drug-drug interactions that should be avoided in older adults (Beers Table 5)' (12).

According to 2019 Beers Criteria Table 2, PIPs are listed under 3 categories which are anticholinergics, antiparkinsonian agents and central nervous system drugs. Tricyclic antidepressants (TCAs), paroxetine, first and second generation antipsychotics (use other than of psychotic disorders and bipolar disorders and cognitive impairements with severe behavioral problems), anticholinergic drugs, barbiturates, short, intermediate and long-acting benzodiazepines (use other than of severe general anxiety disorder, ethanol withdrawal or rapid eye movement sleep behavior disorder) and non-benzodiazepine benzodiazepine receptor agonists (Z drugs) are considered as PIPs (12).

Patient's Diagnosis

The patients were grouped according to their ICD-10 (International Classification of Diseases 10th version) diagnosis. Since Beers Criteria 2019 recom-

mended antipsychotics use only in psychotic disorders and bipolar disorders and there were limited number of those patients, these two groups of patients were united. Similarly, due to the limited number of participants with the diagnosis of anxiety disorders and obsessive-compulsive disorder (OCD), these patient groups were also reunited. Other patient groups were comprised of depressive disorders, cognitive impairments (including Alzheimer's Disease, frontotemporal dementia, and mild cognitive impairment), and sleep disorders.

Statistical Analysis

The data was analyzed using the Statistical Package for Social Sciences (SPSS) for Windows version 20.0. Normally distributed variables were tested by Kolmogorov-Smirnov Test. Descriptive statistics of the numerical data were arranged as the median, interquartile range (Q1-Q3) since they did not show normal distribution. The chi-square test was used to evaluate the relationships between the categorical variables and the Mann-Whitney U test was used for non-parametric variables. For the multivariate analysis, the possible factors identified with chi-square and Mann-Whitney U test were further entered into the logistic regression analysis. Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. A 5% type-I error level was used to infer statistical significance.

RESULTS

A total 235 out of 281 patients formed the study group. Among the participants, 65% (n=153) of them were female and 35% (n=82) of them were male. The mean age (±SD) of the study group was 73.95 ± 7.30 years, ranged from 65 to 97 years. The diagnosis of the patients was given in Table 1.

The median number of psychiatric drugs and total drugs used were 1.8± 0.88 (min-max; 1-4) and 5.14 ± 1.90 (min-max; 1-11), respectively. The rate of drug-drug interactions was found in 20.9% of the

patients. All of the drug-drug interactions were due to the ≥3 psychotropics use according to Table 5 of Beers Criteria 2019.

The rate of at least one PIPs use according to Beers Criteria 2019 was 35.7% (n = 84). The three most commonly prescribed PIPs were antipsychotics (52.4%) (quetiapine (47.8%), risperidone (22.7%), haloperidol (15.9%), aripiprazole (6.8%), sulpiride (4.5%), and zuclopenthixol (2.3%)), benzodiazepines (20.2%) (alprazolam (58.9%), clonazepam (17.6%), lorazepam (17.6%) and diazepam (5.9%)) and, antidepressants (17.9%) (paroxetine (46.75%), amitriptyline (20%), clomipramine (20%), imipramine (13.3%)). Other less commonly prescribed PIPs were anticholinergic agents (6%) (hydroxyzine (80%), diphenhydramine (20%)) and non-benzodiazepine hypnotic drugs (3.6%) (zopiclone (100%)) (Table 1).

When the PIPs users were compared to non-PIPs users, female gender, the total number of psychotropics and total drugs used were significantly higher in PIPs users. On the other hand, PIPs use was significantly less common in patients with psychotic&bipolar disorders and cognitive impairments. The rate of drug-drug interactions and the number of comorbid medical illnesses were not statistically significant between the groups (Table 2).

According to the results of logistic regression analysis, the total number of drugs used, the number of psychotropic drugs used, and psychiatric diagnoses were important predictors of PIPs use (p<0.05). One unit increase in the total number of drugs increased the probability of PIPs use 1.2 times. Similarly, one unit increase in the number of psychotropic drugs increased the probability of PIPs use 3.6 times. A diagnosis of psychosis and cognitive impairment reduced the risk of PIPs use by 91% and 97%, respectively, compared to a diagnosis of depression (Table 3).

DISCUSSION

This study revealed that the rate of at least one PIPs use and drug-drug interactions were high among the elderly outpatients with a psychiatric diagnosis. Antipsychotics were the main group of drugs used as PIPs. Our study also showed that drug-drug interactions in those patients were caused by multiple (≥3) psychotropics use. The total number of drugs and psychotropics was significantly higher in patients who use PIPs compared to non-PIPs users. In multivariate analysis, the PIPs use was associated with the number of psychotropic drugs and total medications.

The rate of PIPs use was found as 35.7% in our study. The prevalence of PIPs use has been reported in a wide range of 28-58.5% in the literature (9, 13). This wide range might be due to the assessment tool that was used for screening PIMs and the variety of participant profiles (for ex: general population, psychiatry inpatients or outpatients). There are different guidelines developed by different countries and medical associations to assess inappropriate drug use such as the SAFEs (Frail Elderly Subjects:

Table 1. Psychiatric diagnoses of the patients and the groups of potentially inappropriate psychotropics (PIPs) used by the patients

Psychiatric Diagnosis	n (%)
Depressive Disorders	83 (35.3)
Anxiety Disorders	64 (27.2)
Cognitive Impairments	43 (18.3)
Psychotic and Bipolar Disorders	32 (13.6)
Sleep Disorders	13 (5.5)
Total	**235 (100)**
The groups of PIPs	**n (%)**
Antipsychotics	44 (52.4)
Benzodiazepines	17 (20.2)
Antidepressants	15 (17.9)
Anticholinergics	5 (6)
Non-benzodiazepine hypnotics (Z-drugs)	3 (3.6)
Total	**84 (100)**

Table 2. Comparison of potentially inappropriate psychotropics (PIPs) users and non-PIPs users in terms of sociodemographic and other clinical variables

	PIPs use			
	No n=151 (64.3%)	**Yes** n=84 (35.7%)	**X^2/ z**	**p**
Age (median [Q1-Q3])	70 [67.7-77]	73 [69-81]	-1.761	0.078[a]
Gender n (%)				
Female	91 (60.3)	62 (73.8)	4.359	**0.037[b]**
Male	60 (39.7)	22 (26.2)		
Total number of drugs (median [Q1-Q3])	4 [3-4]	6 [5-7]	-3.169	**0.002[a]**
Number of psychotropic drugs (median [Q1-Q3])	1 [1-2]	2 [1-3]	-3.797	**<0.001[a]**
Number of comorbid medical illnesses (median [Q1-Q3])	1 [1-2]	2 [2-3]	-1.053	0.292[a]
Drug-drug interactions n (%)				
Yes	30 (19.9)	19 (22.6)	0.248	0.619[b]
No	121 (80.1)	65 (77.4)		
Psychiatric Diagnosis n (%)				
Depressive Disorders	45 (29.8)	38 (45.2)		
Anxiety Disorders	38 (25.2)	26 (31.0)		
Psychotic and Bipolar Disorders	26 (17.2)	6 (7.1)	20.985	**<0.001[b]**
Cognitive Impairments	37 (24.5)	6 (7.1)		
Sleep Disorders	5 (3.3)	8 (9.5)		

n= number of patients; a= Mann-Whitney U Test; b=Chi-square test

Table 3. Multivariate analysis of factors related to use of potentially inappropriate psychotropics (PIPs)

	OR	**95% CI**	**p**
Gender			
Female	0.723	0.362 – 1.447	0.360
Male			
Total number of drugs	1.197	0.997-1.438	**0.044**
Number of psychotropic drugs	3.619	2.157-6.072	**<0.001**
Psychiatric Diagnosis			
Depression		*Reference*	
Anxiety disorders	0.900	0.426-1.898	0.781
Psychotic and Bipolar Disorders	0.092	0.026-0327	**<0.001**
Cognitive Impairments	0.028	0.007-0.110	**<0.001**
Sleep Disorders	0.366	0.479-7.344	0.366

OR: Odds ratio; CI: Confidency Interval; Dependent variable: PIPDU Cox & Snell R^2 =0,251; Nagelkerke R^2 =0,345; -2 Log likelihood = 238,421

Evaluation and follow-up in France), STOPP/START criteria developed in Ireland, and PRISCUS list used in Germany (13-15). Although their contents mostly overlap, the change of drug lists as a result of differences in experts' opinions and updates may be reflected in the studies as different prevalences. Additionally, the rates of PIPs prescriptions differed in patient groups and were found to be higher in hospitalized or nursing-home patients than outpatients (16). Our results of PIPs use rate was in line with the studies in the literature, and this high rate revealed that one out of every three elderly patients with a psychiatric disorder uses PIPs.

According to our study, the most commonly prescribed PIPs were antipsychotics. Although the most used PIPs in the elderly varied in previous studies, hypnotics, antipsychotics, and antidepressants were reported as the most common psychotropic agents used in these patients (7, 13, 17). It was stated that hypnotics/benzodiazepines were the most common psychotropics used in hospitalized and community-dwelling geriatric patients (13, 18). However, as shown in our study, antipsychotics were reported as the main group of drugs prescribed for elderly adults in outpatient clinics (7). It has been reported that the use of antipsychotics is associated with an increased risk of stroke, pulmonary embolism, and hip fractures in the elderly population (19-21). Because of these risks, Beers Criteria emphasize that the use of antipsychotics should be avoided in geriatric patients except in patients with schizophrenia, bipolar disorder, and dementia for whom non-pharmacological treatment is inadequate (12).

It has been shown in studies for a long time that benzodiazepines, anticholinergic agents, and antidepressants with high anticholinergic activity are associated with cognitive decline, delirium and falls in geriatric patients (16). According to our study, benzodiazepines are the second most commonly used PIPs, it might be because there are few options other than benzodiazepines for the treatment of acute or severe psychiatric conditions. However,

the low rate of anticholinergic agent use may indicate that clinicians have a high level of awareness in this context.

Another finding of this study was PIPs use was significantly more common in females. Previous studies reported that the female gender is an independent risk factor for PIMs use (22). This situation may be related to the more common and atypical course of some psychiatric disorders in female patients, and the fact that female patients may seek more help. Although in some studies the older age was shown as a risk factor for PIPs use (13), there was no statistically significant difference in terms of age between PIPs users and non-PIPs users.

Similarly, we could not observe a higher risk among diagnostic groups for receiving PIPs. There are studies showing that depressive and anxiety disorders are at high risk for the use of PIPs (16), while some researchers showing that the prevalence of PIPs use in these groups is not different from other patient groups (23). Moreover, the significantly less use of PIPs in psychotic disorder, bipolar disorder, and cognitive impairments might be due to the Beers' criteria approving the use of some antipsychotic drugs in these patient groups.

In our study, the rate of drug-drug interaction was found as 20.9% and all the interactions were due to the ≥3 psychotropics drug use. On the other hand, there was no significant difference in drug-drug interaction rates between the PIPs user and non-PIPs user groups. In a previous study, there was not found a relationship between inappropriate medication use and ADRs (7). These results reveal that the use of multiple psychotropic agents is an important risk factor for drug-drug interactions and ADRs, even in the absence of inappropriate medication use.

In multivariate analysis, the use of PIPs was found to be associated with the number of psychotropic drugs and total medications. Along with similar lines, the number of drugs used and polypharmacy were reported to be associated with PIMs

in previously published studies (7, 24, 25). By contrast, the relationship between the prescription of PIPs with the number of psychotropics used by the patients was not stated in the previous studies. The number of psychotropic drugs used was shown to increase the PIPs risk 3-times more than the total number of medications taken. Additionally, multiple use of psychotropics might lead to important drug-drug interactions that are recommended to be avoided in the elderly population. In some cases with poor treatment response, the clinicians might feel helpless and in need of additional medication prescribing. However, according to our study results it should be considered in clinical practice that every psychotropic drug added to the treatment list brings significant risks for the patient.

This study has certain limitations. It was a single-centered cross-sectional study with limited patients which make it difficult to generalize the result of the study to the population. However, the study center was one of the main mental health hospitals in Turkey that accept patients from different regions of the country. Although we confirmed the use of medications both from the patients themselves and the electronic health database, we have no certain information on whether they use declared medications regularly. Furthermore, we could only assess a limited number of variables associated with PIPs use, as other factors of interest such as physician characteristics or reasons for the choice of the medications.

In conclusion, PIPs use is highly common in psychiatric elderly outpatients. Geriatric patients constitute an important proportion of daily practice. Therefore, evidence-based medicine tools are important guidelines for a safer and better quality prescription in this vulnerable population. Rational reduction of the number of prescriptions and more effective use of nonpharmacological psychotherapeutic interventions may raise the quality of life and reduce the risk of ADRs in geriatric patients.

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