Polypharmacy and Potential Drug Interactions Causing Neurological Symptoms in Geriatric Patients with Epilepsy

Bahar Erbaş

Department of Pharmacology, Demiroğlu Science University, Faculty of Medicine, İstanbul, Türkiye
Department of Neurology, Ataşehir Florence Nightingale Hospital, İstanbul, Türkiye

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Corresponding author: Bahar Erbaş, e-mail: baharerb@yahoo.com

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Abstract

Objective: Polypharmacy brings with it the risk of potential drug interaction. This study aimed to investigate polypharmacy, potential drug interactions, the drug interactions causing neurological symptoms in geriatric patients with epilepsy, and diffenrences between drug interaction databases.

Methods: The study included patients with epilepsy aged 65 and over (the demographic information, antiepileptic drug use, other chronic diseases, and medications of the patients were retrospectively recorded from their files). The use of 5 or more drugs was accepted as polypharmacy. Potential drug interactions were checked from 2 open access databases (database-1; database-2), and interacting drugs, interaction types, clinical results, and differences between databases were determined.

Results: This study included 126 patients (56 females/70 males), the mean age was 73.13 ± 7.42 (65-92), and the mean duration of antiepileptic drug (69.8% monotherapy) use was 9.08 ± 13.68 (0.5-58) years. The most commonly used antiepileptic drug was levetiracetam (69.8%). Totally 88 patients had at least 1 central nervous system disease (except epilepsy), and 116 had a chronic diseases other than central nervous system disease. Polypharmacy frequency was 75.4%. The most commonly used drug groups with the highest potential drug interaction risk were antihypertensives (69%), antiaggregant-anticoagulants (67%), statins (44%), proton pump inhibitors (41%), and antidepressants (39%). The major, intermediate, and minor potential drug interactions for database-1 and database-2 were 44 versus 53; 586 versus 428, and 127 versus 70, respectively. The most important potential drug interactions were the increased risk of hemorrhage and thrombotic events, arrhythmia, and blood pressure changes.

Conclusion: It is important to know about potential drug interactions (especially involving cardiac drugs, antidepressants, statins, and proton pump inhibitors) in the evaluation of the entire neurological picture of geriatric epilepsy patients.

Keywords: Drug interactions, epilepsy, polypharmacy

INTRODUCTION

Polypharmacy in geriatric patients is a common condition that carries the risk of drug interactions. Potential drug interactions (PDIs) are possible interactions between drugs used, regardless of whether the interaction occurs clinically in the patient and is basically divided into 2 main groups as pharmacokinetic (PK) and pharmacodynamic (PD) interactions.[1,2]

The treatment of epilepsy in the elderly requires special attention due to the etiology, comorbidities, sedative, and anticholinergic effects of drugs, polypharmacy, and changes in the PK and PD of drugs that may be caused by aging.[3] First-generation antiepileptic drugs (AEDs) (carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB), primidone (PM)) are the most risky AEDs in terms of drug interactions in the treatment of epilepsy, and these drugs induce some other enzymes related to drug metabolism in the liver, as well as cytochrome P450 (CYP-450).[2,3] Valproic acid (VPA) inhibits some CYP-450 enzymes and several other enzymes.[2] In current epilepsy treatment, the tendency of clinicians to use AEDs has changed in favor of new-generation AEDs that are less involved in drug interactions.[4-6] Since the response of epilepsy to monotherapy is high in elderly patients (80%-85%), interactions between AEDs and other drugs or between other drugs gain importance in terms of changes in the neurological picture, rather than interactions between AEDs.[4,7]

There are many open-access databases or databases with subscription used to detect potential drug interactions.[8-10] These databases (DBs) generally indicate which drugs interact at what level of severity and through which mechanisms. However, there may be differences between DBs in terms of the drugs they contain in their list, the presence of interaction, and the grading of its severity.[9-12] Open-access DBs may be preferred due to their ease of access.[8,12]

Our primary aim in this study was to determine the frequency of polypharmacy and to investigate PDIs causing neurological symptoms mimicking/complicating the evaluation of epilepsy (seizure, altered consciousness, syncope, dizziness-instability, transient focal deficits, sleep/movement

disorders, cognitive disorders, etc.) resulting from conditions such as hypertension, hemorrhage-ischemia, central nervous system (CNS) involvement (cognitive, etc.), and electrolyte changes in epileptic patients aged 65 and over. Our secondary aim is to show that there may be differences between the databases used for drug interactions and to give an idea about the databases that epilepsy clinicians can use when controlling drug interactions.

METHODS

Elderly patients (≥65 years of age) visiting our neurology outpatient clinic between January 2019 and December 2021 and were taking AEDs with the diagnosis of epilepsy or were started on AED treatment for epilepsy were included in the study. Demographic data of the patients, duration of epilepsy and AED use, comorbidities, and drugs given for use for 3 months or longer were recorded retrospectively from the patient files. The use of 5 or more drugs was accepted as polypharmacy.[13,14] Potential drug interactions were controlled using 2 of the most frequently used open-access DBs in the literature.[8,12] The first database (DB-1) "Drugs.com: Intreaction Checker" and the second database (DB-2) "Medscape: Drug Interaction Checker" were used. The 2 databases we used rank the severity of drug interactions differently. Potential drug interactions are categorized as "major, moderate, and minor" according to DB-1, and as "serious, requiring close monitoring and minor" according to DB-2. Definitions of PDI severity categories in DB-1 were "clinically very significant, the combination should be avoided as the risk of interaction outweighs the benefit" for major PDIs, "clinically significant, their combination should generally be avoided but used in special circumstances" for moderate PDIs and "clinically minimally significant, alternative medicine should be considered by evaluating the risk and/or a monitoring plan should be established" for minor PDIs. There is no definition on the web page for the PDI categorizations of DB-2. Although it is estimated that there are differences in the drug lists included by both DBs, there is no research on which drugs these differences cover.

In our study, according to the results obtained from DBs, the drugs and drug groups with the highest potential for interaction, interaction types, and clinical results, as well as differences between DBs, were determined. The number of PDIs per patient that may affect the neurological presentation was calculated.[15] Local ethics committee approval was obtained for the study (Demiroğlu Bilim University Clinical Research Ethics Committee; decision date: December 14, 2021; decision No: 14.12.2021/ 2021-25-03. Appendix decision date: April 05, 2022; decision no: 05.04.2022/2022-07-09).

Regarding the pharmalogical classification of PDIs, interactions "involving changes in drug metabolism, absorption, distribution, renal excretion, and serum concentration" are classified as PK interactions and interactions "occuring at the site of action of the drug, which can alter the therapeutic and toxic effect (synergistically or antagonistically)" are classified as PD interactions.[2]

Statistical Analysis

The data were transferred to the computer and were analyzed by the statistical program Statistical Package for the Social Sciences version 21.0. (IBM SPSS Corp.; Armonk, NY, USA). Number, percentage, mean, and standard deviation were used as descriptive statistics. Student's *t* test was used to investigate the differences between the groups, since the data showed normal distribution. $P < .05$ was accepted as statistical significance level.

RESULTS

This study included 126 patients, and the mean age was 73.13 ± 7.42 (65-92). Demographic data of these patients and information about other chronic diseases are given in Table 1. In most of the patients, at least 1 CNS disease and a chronic disease related to other systems were detected other than epilepsy (Table 1). The mean duration of AED use was 9.08 ± 13.68 (0.5-58) years.

Polypharmacy was found in 95 (75.4%) patients, and this number increased to 106 (84.1%) when the vitamins and nutritional supplements they took were added. It was observed that 88 patients (69.8%) used at least 1 CNS drug other than AEDs, the average number of drugs per patient was 5.51 ± 2.96 (0-12), and when nutritional supplements were added, the number was 7.30 ± 3.37 (1-17). The drug information of the patients and PDIs that may cause neurological symptoms are listed in Table 2.

Major PDIs according to DB-1 and DB-2 are shown in Table 3 and differences between both databases in all PDI categories are shown in Table 4. The distribution of the number of moderate PDIs detected in DB-1 according to drug groups is as follows: 364 cardiovascular

MAIN POINTS

- One of the primary aims of the study was to determine the rate of polypharmacy in geriatric epilepsy patients. The rate of polypharmacy was found to be rather high (75.4%), and this rate increased to 85% when nutritional supplements were added. The rate of polypharmacy was found to be higher than many other studies in the literature.
- The other primary aim of the study was to evaluate the increased risk of potential drug interactions with polypharmacy, which may affect the neurological clinical status (seizure, altered consciousness, syncope, dizziness imbalance, temporary focal deficits, sleep/movement disorders, cognitive disorders, etc.) in the geriatric epilepsy patients.
- It was observed that the most used antiepileptic in our patients was levetiracetam (69.8%), the rate of use of new-generation antiepileptics, which do not affect the cytochrome P450 enzyme system, was high, and seizure control could be achieved with monotherapy in most patients (69.8%). For this reason, pharmacokinetic drug interactions involving antiepileptics are much less than other drug groups.
- The frequency of drug interactions of the drug groups (other than antiepileptic drugs (AEDs)) used at the same time by geriatric epileptic patients (especially antidepressants, cardiac drugs, and antiaggregant/anticoagulants) was higher than AEDs. A significant number of these potential drug interactions carry the risk of altering neurological status. It has been emphasized that some drug groups such as statins, proton pump inhibitors, and alpha blockers (used in benign prostatic hypertrophy), which are frequently used in this age group, may be overlooked by physicians and patients and that these drugs may also have important interactions.
- Our secondary aim was to inform clinicians dealing with epilepsy about drug interaction databases and to show that there may be differences between them. Databases are often used to determine potential drug interactions. It was seen that some drugs were not found in both databases used in this study, and there were differences between interaction types and the grading of interaction intensities. Similar results have been shown in some previous studies. Therefore, it is important to check potential drug interactions from more than 1 database and the clinicians should reassess the results with their pharmacology knowledge.

Table 1. Demographic Information of Patients and Chronic Diseases

	n (%)
Number of patients	Total 126; 56 females (44.4%); 70 males (55.6%)
Other CNS diseases	**88 (69.8%)**
	Stroke: 44 (34.9%), neurodegenerative diseases: 31 (24.6%) (most common Alzheimer's dementia), psychiatric diseases: 51 (40.5%) (most common depression), intracranial mass (operated or not): 32 (25.4%), others (insomnia, vertiginous syndromes): 17(13.5%)
Non-CNS chronic diseases	**116 (92.1%)**
Cardiovascular diseases	HT: 74 (58.7%), HL: 56 (44.4%), CHD: 43 (34.1%), DM: 38 (30,2%), dysrhythmia: 26 (20.6%), CHF: 23 (18.3%)
Others	GIS: 29 (23%), thyroid diseases: 28 (22.2%), other endocrine diseases: 2 (1.6%), BPH: 24 (19%), lung diseases: 5 (3.9%), non-CNS malignancy: 8 (6.3%), rheumatological diseases: 4 (3.2%), others: 13 (10.3%)

BPH, benign prostatic hyperplasia; DM, diabetes mellitus; GIS, gastrointestinal system; HL, hyperlipidemia; HT, hypertension; CHD, coronary heart disease; CHF, congestive heart failure; CNS, central nervous system.

system (CVS) drugs, 283 CNS drugs other than AEDs, 177 AEDs, 51 oral antidiabetics (OAD), and 35 lipid-lowering drugs. It was determined that lercanidipine and some OADs were absent in both databases. The number of PDIs per patient (per patient) that may affect the neurological presentation is 6.01 ± 4.87 (0-21) according to DB-1 and 4.33 ± 3.82 (0-15) according to DB-2. The number of PD PDIs was significantly higher than the number of PK PDIs in both databases ($P < .001$) (Table 4).

Potential major and moderate drug interactions found in our patients' file records are given as follows: 6 major PDI [myopathy due to combined use of statin and fenofibrate in 1 patient, hypotensive syncope due to concomitant use of citalopram and quetiapine in 1 patient, arrhythmia due to combined use of risperidone and amiodarone in 1 patient, hemorrhage (gastrointestinal and intracranial) due to acetylsalicylic and anticoagulant use in 2 patients, hyponatremia due to carbamazepine-diuretic combination in 1 patient], 14 moderate

Table 2. Drugs Used by Patients in Chronic Diseases, Potential Drug Interactions That May Affect the Neurological Status, and Drug Groups That May Interact with Each Other

	n (%)
Number of AEDs	Monotherapy 88 (69.8%), dual therapy 36 (28.6%), polytherapy 2 (1.6%)
DRUGS	
CNS drugs	LVT 88 (69.8%), CBZ 18 (14.3%), LCM 17 (13.5%), LTG 13 (10.3%), VPA 8 (6.3%), OXC 7 (5.5%), other 8 (TPM-CLZ-PHT-GBP) (6.3%)
Antiepileptic	
Antidementia	AChEİ 20 (15.9%), memantin 11 (8.7%)
Antidepressant	SSRİ 39 (31%) (mostly escitalopram), SNRİ 4 (3.2%) (duloxetine), serotonin modulators 3 (2.4%) (vortioxetine), other 3 (2.4%) (amitriptyline, trazodone)Atypical AP 10 (7.9%) (mostly quetiapine), typical AP 1 (0.8%) (haloperidol)
Antipsychotic	
Anti-Parkinson	Levodopa 5 (4%), DA 4 (3.2%), MAO B inh. 1(0.8%)
Other	5 (4%) (mostly melatonin)
CVS drugs	BB 55 (43.7%) (mostly metoprolol), ACEİ - ARB 51 (40.5%) (mostly ramipril and losartan), CCB 37 (29.4%) (mostly amlodipine), diuretic 33 (26.2%) (mostly HTZ), AB 11 (8.7%) (doxazosin), A&BB 4 (3.2%) (carvedilol)
Antihypertensive	
Antidysrhythmic	Antidysrhythmics that is not specified in another drug group in the table: 3 (2.4%) (2 propafenone, 1 amiodarone)
Anticoagulant	ASA 45 (35.7%), clopidogrel 6 (4.8%)
Antidiabetics	NOAC 23 (18.3%) (mostly rivaroxaban), warfarin 11 (8.7%)Metformin 19 (15.1%), sulfonylurea 10 (7.9%), insulin 7 (5.5%), gliptin 7 (5.5%), glitazone 5 (4%), SGLT-2 inh. 3 (2.4%),Statin 56 (44.4%) (mostly atorvastatin), fibrate 4 (3.2%)
Antidyslipidemics	
Other drugs	**GIS drugs**—PPI 52 (41.3%) (mostly pantoprazole), **Thyroid hormone** 25 (19.8%) (levothyroxine); **BPH drugs**—AB 24 (19%) (mostly silodosin), **Other** 13 (10.3%)
PDI types by clinic	***Interacting drug groups (drug combinations)***
Dysrhythmia (mostly bradycardic)	AChEIs, antidysrhythmics/cardiac drugs causing bradycardia (BB, CCB*, digoxin)-some AEDs (e.g., sodium channel blocker such as LCM and PHT), antidepressants such as SSRIs/TSAs, antipsychotics, fingolimod, oxaliplatin, hydroxychloroquine.
Hypotension	Combination of all anti-HTs with each other or with dopaminergic drugs (L-dopa, etc.), antidepressants (SSRI, etc.), antipsychotics, ABs used in BPH.
Hypertension	Concomitant use of SNRI/SSRI/TSA (serotonin synd.); **Decreased anti-HT effect:** EIAEDs-dihydropyridine CCB (amlodipine etc.); antiHT-ASA combinations
Hemorrhage	Combinations of antiaggregant/anticoagulants with each other or with SSRIs /VPA; EIAEDs (CBZ, PHT, PB) with warfarin
Ischemia	Concomitant use of clopidogrel and the drugs inhibiting CYP450 3A4 [fibrates, some statins, CCBs, BBs, PPIs (omeprazole / esomeprazole etc.)]
Electrolyte change	**Hyponatremia:** Diuretics with SSRI/SNRI/vortioxetine; **Hyperkalemia:** K-sparing diuretics with ACEI-ARB, **Hypomagnesemia, hypocalcemia:** PPI with Diuretics
Other	**Lactic acidosis**: diuretic-metformin; **myopathy:** combination of statins-fibrates with each other or with glitazone group OADs/some PPIs; **hyperthermia-oligohidrosis:** carbonic anhydrase inh. (e.g., topiramate)-anticholinergic drugs (e.g., quetiapine)

*Non-dihydropyridine CCBs. A&BB, alpha-beta bl.; AB, alpha bl.; ACEI, angiotensin converting enzyme inh.; AChEI, acetylcholine esterase inh.; AD, antidepressant; AED, antiepileptic drug; AntiHT, antihypertensive; AP, antipsychotic; ARB, angiotensin receptor bl.; ASA, acetylsalicylic acid; BB, Beta bl.; BPH, benign prostatic hyperplasia; CCB, calcium channel bl; CVS, cardiovascular system; CNS, central nervous system; DA, dopamine agonist; GIS, gastrointestinal system; HT, hypertension; HTZ, hydrochlorothiazide; NOAC, new oral anticoagulants; PDI, potential drug interaction; PPI, proton pump inhibitors; SGLT, sodium glucose transporter; SSRI, selective serotonin reuptake inhibitors; Synd, syndrome.

Table 3. Major (Serious) Potential Drug Interactions and Differences Between Databases

Drug interactions common to both databases and classified as major (serious)		
Interacting Drugs (n)	**Clinical Effect**	**Interaction Type**
CBZ–quetiapine (7)	Quetiapine effectiveness is reduced	CYP450 3A4 induction/PK
Citalopram–hydroxychloroquine (1)	Dysrhythmia, syncope	QT prolongation/PD
Citalopram–fingolimod (1)		
Citalopram–oxaliplatin (1)		
Escitalopram–trazodone (1)	Serotonin syndrome, dysrhythmia, etc.	Serotonergic overactivity/PD
Fluxetine–clopidogrel (1)	Ischemic event (clopidogrel effectiveness is reduced)	CYP450 2C19 inhibition/PK
Esomeprazole–clopidogrel (1)		
Risperidone–amiodarone(1)	Dysrhythmia, syncope	QT prolongation/PD
Statin–fenofibrate (4)	Myalgia, weakness, urine discoloration	Increased myotoxic effect, increased PC of atorvastatin/PK–PD

Differences in major (serious) drug interactions between databases

DB-1			**DB-2**		
Interacting Drugs (n)	**Clinical Effect**	**Interaction Type**	**Interacting Drugs (n)**	**Clinical Effect**	**Interaction Type**
Topiramate–quetiapine (1)	Oligohidrosis hyperthermia	Anticholinergic-KA effect/PD	CBZ–PPI (7)	PPI activity is reduced	CYP450 3A4 induction/PK
Citalopram–quetiapine (5)	Dysrhythmia, syncope, dizziness	QT prolongation, hypotension/PD	CBZ–atorvastatin (8)	Statin effectiveness is reduced	
Citalopram–PPI (8)	Citalopram increases IE-QT prolongation, hypotension	CYP450 2C19 inhibition/PK	CBZ–clopidogrel (3)	Clopidogrel effectiveness is increased	
Citalopram–fenofibrate (3)			CBZ–esomeprazole (1)	Esomeprazole effectiveness is reduced	CYP450 2C19 induction/PK
Fluoxetine–tamoxifen (1)	Tamoxifen efficacy decreases	CYP450 2C19 inhibition/PK	CBZ–thiazide (2)	Consciousness change, etc.	Hyponatremia/PD
ASA–YOAK (6) ASA–warfarin (2)	Hemorrhage	Potentiation of the effect of drugs/PD	CBZ–silodosin (1)	Silodosin activity is reduced	CYP450 3A4 induction/PK
			ASA–ramipril (5)	HT	Ramipril efficacy is reduced PD
			BB–rivastigmine (8)	Dysrhythmia	Bradyarrhythmia/PD

ASA, acetylsalicylic acid; BB, beta blocker; CA, carbonic anhydrase; CBZ, carbamazepine; PC, plasma concentration; PD, pharmacodynamic interaction; PK, pharmacokinetic interaction; HT, hypertension; PPI, proton pump inhibitors; NOAC, new oral anticoagulants.

PDI (hypotension—dizziness/syncope in 7 patients due to multiple antihypertensive or antihypertensives + citalopram/escitalopram combinations, orthostatic hypotension due to the combination of levodopa and alpha–beta blocker carvedilol in 2 patients, syncope due to BPH drugs + beta-blocker use in 3 patients, hyponatremia due to escitalopram–thiazide diuretic, citalopram–carbamazepine combinations in 2 patients).

Table 4. Differences in the Number of Potential Drug Interactions (PDIs) and Clinical/Pharmacological PDI Types Between the Databases (DB-1 and DB-2)

PDI types	**DB-1**	**DB-2**	***P***
Number of major (severe) PDIs	44	53	>.05
Number of moderate PDIs	586	428	**.004**
Minor number of PDIs	127	70	**.003**
Total number of PDIs	757	551	**.002**
Clinical PDI type			
Dysrhythmia	120	57	**<.001**
Hypotension	164	126	>.05
Hypertension	79	76	>.05
Ischemia	20	15	>.05
Hemorrhage	61	62	>.05
Electrolyte changes	61	54	>.05
CNS involvement (cognitive, etc.)	120	42	**<.001**
Other (myopathy, etc.)	44	44	>.05
Total PDI that may affect the neurological status	669	476	**.005**
Pharmacological PDI type*			
Pharmacodynamic	585	398	**.002**
Pharmacokinetic	172	135	>.05

*35 drug interactions are specified separately as pharmacodynamic and pharmacokinetic in DB-2.
Bold values are statistically significant

DISCUSSION

Polypharmacy in epileptic patients is higher than in the general population.[15] In the study by Bruun et al[15], the frequency of polypharmacy in geriatric epilepsy patients was found to be 69% and the number of non-AED drugs used was 7.64. In addition, polypharmacy involving CNS drugs has been increasing in the elderly in recent years.[16] The rate of polypharmacy in this study was even higher than in some studies in the literature.

The rate of monotherapy in the treatment of epilepsy was found to be 69.8% in our study, and the most commonly used antiepileptic was levetiracetam (LVT). In the study by Stefan et al.[17] it was found that patients with epilepsy above 65 years of age needed less AEDs than younger epilepsy patients (<50 years), and the most commonly used AED was LVT (25.3%). In studies up to the early 2000s, it is seen that the most used drugs in the elderly were PHT and CBZ, and in later studies, the preference shifted to second-generation AEDs (e.g., LVT and lamotrigine–lamotrigine [LTG], etc.).[4-6,18] For elderly patients, it may be more appropriate to choose second- and third-generation AEDs with less risk of drug interaction than AEDs with a narrow therapeutic

window.[2,5] In the case of multiple AED use (especially sodium channel-blocker CBZ, oxcarbazepine (OXC), LTG, lacosamide), CNS side effects may increase through PD interactions.[2]

It has been demonstrated in this study that potential PD drug interactions between drugs used by elderly epileptic patients, which may mimic neurological symptoms, are more frequent than with PKs. The most important mechanisms of PK interactions are the effects of CYP-450 enzymes, which are involved in drug metabolism in the liver, and permeability glycoproteins (P-gp), which regulate the absorption of drugs from the intestine, hepatic and renal excretion, and their passage through the blood–brain barrier.[2,19] Interactions related to protein binding and drug distribution are especially important in hypoalbuminemia and high protein-binding drugs (e.g., PHT, VPA).[2] Regarding the drugs used frequently in this age group, it should be kept in mind that acetylcholine esterase inhibitors (AChEIs) and memantine do not interact significantly via CYP-450, but many antipsychotics, selective serotonin reuptake inhibitors (SSRIs) [e.g., fluvoxamine, paroxetine and fluoxetine, sertraline (to a lesser extent)], proton pump inhibitors (PPIs) (e.g., omeprazole and esomeprazole), some antiarrhythmics (e.g., amiodarone, verapamil) and statins (e.g., fluvastatin, lovastatin, pravastatin) may interact with many drugs through CYP-450 enzymes.[20-26] Additionally, many antidepressants, antipsychotics, antihypertensives (especially dihydropyridine calcium-channel blockers (CCB)), and antihyperlipidemics can interact even if they do not induce or inhibit CYP-450, since they are metabolized via CYP-450.[21] Pharmacodynamic interactions occur at the drug's site of action and may alter the therapeutic and toxic effect (synergistically or antagonistically) but do not affect the serum concentration of the drug.[2] The risk of PK PDI is higher with enzyme-inducing AEDs (EIAEDs). Second- and third-generation AEDs rarely interact with other drugs in the PK type.[3,15] LTG, topiramate (TPM), eslicarbazepine, felbamate, rufinamide, perampanel, and OXC are mild and dose-dependent (e.g., TPM ≥ 200 mg, LTG ≥ 300 mg, perampanel ≥ 8 mg) enzyme inducers, but they are generally categorized as "non-enzyme-inducing" AEDs in studies.[2,27]

In our study, there were only 8 major PDIs related to AEDs (7 with CBZ, 1 with topiramate), and antidepressants were the most common drug group in major PDIs. As for medium and minor PDIs, the most prominent groups of drugs in terms of frequency were antidepressants and cardiac drugs.

Antidepressants that change the metabolism of antiepileptic drugs the least are citalopram, escitalopram, venlafaxine, and duloxetine.[28] Although SSRIs are the most widely used antidepressants with an advantageous safety profile in the elderly, they can increase the effects of CBZ, PHT, VPA, many beta-blockers (BB), antidysrhythmics, and warfarin by inhibiting their metabolisms via CYP2D6.[2,27,29-31] Escitalopram and citalopram interact least with AEDs in this respect.[30] Since serotonin release from platelets plays a role in hemostasis, drugs that inhibit serotonin reuptake (especially SSRIs) may increase the risk of bleeding by potentiating the effect of antiaggregants and anticoagulants.[31] In addition, the use of many antidepressants with some CNS and CVS drugs creates a risk of hyponatremia, serotonin syndrome, dysrhythmia, and hypotension.[31-36]

Potential drug interactions that can cause clinical dysrhythmias may result from combinations of AChEI, antidysrhythmic/bradycardia-inducing cardiac drugs (BB, non-dihydropyridine CCB, digoxin, etc.), some AEDs (e.g., sodium channel blockers), antidepressants (especially certain SSRIs/TSAs), and most of the antipsychotics.[2,20,29,32-34,37-39] Proton pump inhibitors (omeprazole, esomeprazole) that inhibit CYP2C19 can cause dysrhythmia when used with TSAs, citalopram, and escitalopram.[22,23]

Potential drug interactions causing hypotension may occur with the use of multiple antihypertensive and/or combinations of antihypertensives, antidepressants, antipsychotics, some antiparkinsonian drugs, and certain other drugs such as alpha receptor blockers used in benign prostatic hyperplasia (BPH) treatment.[20,35,36,40-43] In cases where BBs and alpha blockers (ABs) are used together, the risk of "first dose syncope" that can be caused by ABs increases as BBs prevent reflex tachycardia. It should be kept in mind that the drugs such as tamsulosin and silodosin used in the treatment of BPH also have AB properties.[44] Sodium-glucose co-transporter 2 inhibitor OADs (e.g., empagliflozin) may potentiate the effect of diuretics and other antihypertensives.[45]

In terms of PDIs that may cause hypertension, it is remarkable that EIAEDs reduce the effect of antihypertensive drugs by decreasing the blood level of dihydropyridine CCBs (amlodipine, etc.) by 80%-90%.[2,15]

The major hemorrhagic PDIs are related to multiple antiaggregant–anticoagulant use and clopidogrel.[46-48] In ischemic PDIs, it is noteworthy that clopidogrel metabolism is affected by CYP-450 and that ASA bioavailability is reduced by PPIs (minor PDI).[8-50] Also, since clopidogrel is a pro-drug, CYP2C19 (e.g., fluoxetine, omeprazole, esomeprazole) and CYP450 3A4 inhibitors (e.g., statins atorvastatin, lovastatin, simvastatin, cerivastatin, and some PPIs) may reduce the effectiveness of it.[48,51]

Lansoprazole and pantoprazole are relatively safe for use with clopidogrel compared to omeprazole, or H2 blockers (instead of PPIs) can be used with clopidogrel if necessary.[48,50] Enzyme-inducing antiepileptic drugs may increase the active form of clopidogrel.[50,51] Enzyme (CYP3A4)-inducing AEDs reduce the efficacy of warfarin, which may lead to mortal consequences.[2] Phenytoin may initially increase the efficacy of warfarin and decrease it after a few weeks, while warfarin may increase the PHT level.[2,52] Valproic acid may increase the hemorrhagic effect of warfarin by inhibiting CYP2C9/10 and by a dose-dependent thrombocytopenic effect.[2] In order to monitor these interactions, close International normalized ratio (INR) monitoring should be performed, especially in the first week of drug administration.[2] In terms of other oral anticoagulants, inducers of CYP450 3A4 and P-gp may reduce the efficacy of rivaroxaban, but it is not easy to monitor the efficacy of rivaroxaban.[19,53,54] It has been reported that PHT may decrease the efficacy of dabigatran.[55] There are also studies showing that VPA and OXC can interact with new oral anticoagulants.[19] In addition, especially SSRIs may potentiate the effect of antiaggregants and anticoagulants.[31]

One of the most important condition in terms of drug interactions related to metabolic and electrolyte balance changes is hyponatremia. Concomitant use of diuretics with CBZ, OXC (rarely VPA), and some SSRIs may increase the risk of hyponatremia.[31] Hypomagnesaemia–hypocalcemia may develop when diuretics are used together with PPIs. Hypocalcemia is evident when used with loop diuretics.[56] Regarding hypoglycemia, BBs mask the physiological effects of hypoglycemia and lead to prolongation of hypoglycemia, which can be dangerous, especially in patients using insulin and insulin secretagogue OADs.[57]

As antiepileptic drugs reduce bone mineral density and cause ataxia/dizziness, the possibility of falls and bone fracture increases in the elderly.[7,30] Therefore, when adding a drug to the treatment of elderly

patients, it should be started with a low titration, monotherapy should be maintained as much as possible, and the patients should be closely monitored for blood pressure, cardiac rhythm, anticoagulation, and glycemia control.[3,16,58] In addition, the use of CNS drugs can lead to falls and cognitive and functional impairments.[16]

In this study, some differences were found between the 2 databases that we used. It has also been shown in previous studies that there may be differences in the presence and grading of drug interactions between databases when compared in terms of PDI.[9,10,12] The reason for significantly higher arrhythmia-related PDIs number in DB-1 was that dihydropyridine CCBs counted as arrhythmogenically interacting drugs in DB-1. However, no significant arrhythmogenic/bradyarrhythmogenic effect of this group of drugs has been observed.[59] On the contrary, if the vascular resistance decreases more than necessary with these drugs, only mild to moderate reflex tachycardic effect may occur. Furthermore, the higher PDI count involving the CNS in DB-1 could be attributed to all combined use of CNS drugs recorded as PDI in DB-1. For this reason, it is important for the person interpreting PDI to be knowledgeable in terms of pharmacology, pharmacogenetics, and the degree of clinical reflection of PDIs.

The strength of this study is the collection of data by examining all the files of the patients, not the drug administration data banks, unlike many other studies. Thus, information about drugs and nutritional supplements that are not registered in official or health insurance drug systems could be accessed. The limitations of our study are that this study is retrospective and single-centered, and the interactions of some drugs that were not in both databases could not be evaluated.

CONCLUSION

In conclusion, this study emphasizes that the rate of polypharmacy in geriatric epilepsy patients is high, and using more products such as nutritional supplements/unnecessary vitamins makes this figure higher. The increase in the number of drugs and supplements used with unclear ingredient increases the risk of drug interactions and reduces the drug compliance of patients. Furthermore, if there is a change in the neurological status of elderly epileptic patients, PDIs between the drugs other than AEDs (especially commonly used antidepressants/antipsychotics and cardiac-anticoagulant/antiaggregant drugs) should also be taken into consideration. In addition, since there may be some differences between the DBs used, it is important to check the possible interactions from more than 1 DB, and DB results should be reassessed by clinicians with pharmacology knowledge.

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