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## Co-medication and potential drug interactions among patients with epilepsy

Magdalena Bosak<sup>a,\*</sup>, Agnieszka Słowik<sup>a</sup>, Anna Iwańska<sup>b</sup>, Milena Lipińska<sup>b</sup>, Wojciech Turaj<sup>a</sup><sup>a</sup> Dept. of Neurology, Jagiellonian University Medical College, Krakow, Poland<sup>b</sup> Jagiellonian University Medical College, Krakow, Poland

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## ABSTRACT

**Purpose:** This study aimed to analyze the extent of co-medication and to assess potential interactions between antiepileptic drugs (AEDs) and other drugs among patients with epilepsy.**Methods:** We studied 663 consecutive patients with epilepsy seen in tertiary outpatient clinic. Data on epilepsy and current treatment with AED(s) were collected from structured interview and medical records. Other medications used regularly were classified according to the Anatomical Therapeutic Chemical classification system. Possible drug interactions between AEDs and other drugs were analyzed with the use of IBM Micromedex® database.**Results:** Studied sample included 395 women; 54.5% of subjects were on monotherapy. Enzyme-inducing AED(s) were used by 127 patients (19.2%). Among 265 patients who used medications other than AEDs (40.0% of all subjects), potential major and moderate interactions between AEDs and other drugs were found in 80 patients (30.1%). Most prevalent major interactions included: ethinylestradiol/estradiol - valproate/oxcarbazepine/carbamazepine, sertraline-carbamazepine, and simvastatin-carbamazepine. A total number of currently used medications (OR = 1.26 [1.07–1.48] per one additional medication;  $p = 0.005$ ) and the use of enzyme-inducing AEDs (OR = 2.78 [1.51–5.12];  $p < 0.001$ ) were independent predictors of interactions between AEDs and other drugs.**Conclusions:** Co-medication is common (40%) among patients with epilepsy. Potential major or moderate interactions between AED(s) and other drugs are noted in 30.1% of patients exposed to at least one medication other than AED (12.1% of the entire cohort). The risk of potential interactions increases with the number of medications used chronically and with the use of hepatic enzyme-inducing AEDs.

## 1. Introduction

Management of epilepsy usually involves the long-term use of antiepileptic drugs (AEDs) and a substantial percentage of patients require polytherapy to control their seizures [1]. The use of multiple AEDs poses a risk of drug interactions including enzyme induction or inhibition, alterations in protein-binding and expression of transporter proteins [2]. It may result in decreased efficacy or increased toxicity of AEDs. The use of some older AEDs (e.g. carbamazepine or phenytoin), known as potent hepatic enzyme-inducers is a major source of pharmacokinetic interactions between AEDs and other medications commonly used in elderly population, such as statins, antidepressants or neuroleptics [2–4]. Moreover, patients with epilepsy are at increased risk of comorbidities, including neuropsychiatric and pain disorders [5] and a range of cardiac, gastrointestinal and respiratory disorders [6], which often require long-term pharmacotherapy with additional potential for interactions.

The interactions among specific AEDs used in polytherapy of epilepsy are well known and considered in daily practice. The issue of interactions between AEDs and other medications, however, is less appreciated and rarely studied. Only several studies addressed that problem [7–10] and most of them were limited to the elderly patients with epilepsy which impedes generalization of their findings. Nevertheless, they suggest that interactions between AEDs and other drugs are frequent in elderly – according to the most recent study by Faught et al. [10] interactions that possibly affect efficacy of non-AEDs or AEDs were found in 39% and 29% of prevalent cases, respectively.

Patterns of AED prescribing vary widely worldwide with the most notable example of phenytoin which is frequently used in United States [8] but rarely prescribed in Europe [11]. Common use of phenytoin as the major enzyme-inducing AED may contribute to the regional differences in patterns of potential drug interactions. We believed, therefore, that it would be worthwhile to study the problem of co-medication and drug interactions among Polish patients with epilepsy. We

\* Corresponding author at: Dept. of Neurology, Jagiellonian University Medical College, Botaniczna 3, 31-503 Krakow, Poland.

E-mail address: [magdalena.bosak@uj.edu.pl](mailto:magdalenabosak@uj.edu.pl) (M. Bosak).<https://doi.org/10.1016/j.seizure.2019.01.014>

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hypothesized that the rare use of phenytoin in our population may result in less frequent interactions between AEDs and other drugs. Accordingly, this study aimed to analyze the extent and characteristics of co-medication and to assess potential interactions between antiepileptic drugs (AEDs) and non-AEDs among unselected patients with epilepsy seen in tertiary epilepsy center.

## 2. Material and methods

### 2.1. Study population

The study involved consecutive patients with epilepsy who visited the outpatient epilepsy clinic at the Department of Neurology within University Hospital in Krakow (Poland) between January 2016 and March 2018. The inclusion criterion was the diagnosis of epilepsy established according to the International League Against Epilepsy (ILAE) guideline [12]. Patients who did not use any pharmacological treatment for their epilepsy while visiting the outpatient clinic during the study period were excluded.

Protocol of the study observed the principles of Helsinki Declaration and received approval from bioethical committee of the Jagiellonian University of Krakow. Each patient was informed about the aim and methods of the study and gave the written informed consent to participate. All eligible patients agreed to participate.

### 2.2. Procedures and definitions

Data from medical history and the neurological examination were collected and then updated prospectively. An initial interview was structured and comprised the questionnaire that included information on age, sex, age at the diagnosis of epilepsy, duration of epilepsy and type(s) of seizures. The types of epilepsy (focal, generalized, combined or unknown) were defined in line with the recent ILAE classification [13], according to the history, neurological examination, electroencephalography and neuroimaging (magnetic resonance imaging or computed tomography). Currently used AED(s) and their doses were noted. Hepatic enzyme-inducing AEDs category included phenytoin, carbamazepine, phenobarbital, and primidone (topiramate and oxcarbazepine in large doses can also induce hepatic enzymes but we have chosen not to include them in this category).

During an initial visit within the study period patients were asked to fill the questionnaire related to the co-morbidities and medications used chronically. They were also requested to bring all medications currently used and all available medical documents for the subsequent visit. These data were used to verify and to supplement previous information recalled by patients. Chronic treatment with any medication was defined as the regular use of any medication as prescribed by the physician or according to the dosage information in case of over-the-counter medications over 6 months preceding the first visit in an outpatient clinic during the study period. Most medications were used on daily basis, but any regular use of medication was counted as the chronic one (e.g. medications taken regularly once per week were also included).

Medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system [14]. Additionally, we have divided chronically used medications other than AEDs into medications for somatic or psychiatric disorders. The latter ones included antipsychotics, anxiolytics/hypnotics and antidepressants.

Possible drug interactions were analyzed with the use of IBM Micromedex® Drug Interaction Checking [15] which describes interactions between given medications as ‘contraindicated’ (i.e. drugs are contraindicated for concurrent use), ‘major’ (interaction might be life-threatening and/or require medical intervention to minimize or prevent serious adverse effect), ‘moderate’ (interaction may result in exacerbation of the patient’s condition and/or require an alteration in therapy), ‘minor’ (interaction may lead to an increase in frequency or severity of the side effects but generally would not require a major

alteration in therapy) or ‘unknown’. Because of the number of patients and medications used, we have limited our analysis to major or moderate drug interactions. In rare instances of medications not included in Micromedex®, we have used medication leaflets to search for interactions; these interactions were classified as ‘moderate’ if no specific data on severity of potential interactions were found. Additionally, we have retrospectively reviewed product information of each AED used in our patients to make sure that no significant interaction was missed. If more than one type of drug interaction was noted in one patient, it was counted as the clinically more important one (i.e. major, not moderate). Only interactions between AED(s) and other medications were evaluated. In each patient with identified potential major or moderate interaction, the intervention to minimize the risk was subsequently undertaken in cooperation with the referring physician.

### 2.3. Statistical analysis

Variables were characterized with median and interquartile range ( $q_1$ – $q_3$ ), due to their skewed distribution. The significance of the differences between groups was tested with  $\chi^2$  for categorical variables (Fisher exact test was used in comparisons with small absolute number of cases) or with Mann-Whitney  $U$ -test for continuous data.

Predictors of occurrence of major or moderate interaction between AED(s) and other medications (dichotomous dependent variable) were assessed with logistic regression modelling. Initial models were built with all the variables that differed at the level of  $p < 0.1$  in univariate analysis. Models were then optimized using stepwise method (backward selection with determining criterion likelihood ratio for variables selection). A  $p$ -value of less than 0.05 was considered significant for the differences between groups or for variables which entered the final models of logistic regression. All the analyses were performed using Statistica v. 12.5 (StatSoft Inc., Tulsa, OK).

## 3. Results

### 3.1. General characteristics

The study involved 663 patients; the clinical characteristics of the studied group regarding age, sex, age at the onset of epilepsy, type of epilepsy, frequency of seizures and number of currently used AEDs is provided in Table 1. According to the exclusion criteria, each studied patient used at least one AED during the evaluation. Currently used AEDs and their doses are reported in Table 1.

### 3.2. Use of medications other than AED

Two hundred sixty-five patients (40.0%) used at least one medication other than AED. Among them, 219 patients (33.0% of all patients studied) used at least one medication for somatic disorders, 94 patients (14.2%) used at least one medication for psychiatric disorders, and 47 patients (7.1%) used at least one medication for both somatic and psychiatric disorders. One hundred twenty-seven patients (19.2%) took hepatic enzyme-inducing AED(s). Table 2 provides data on numbers of chronically used medications including separate numbers of used AEDs, medications for somatic disorders and medications for psychiatric disorders.

Table 3 shows medications chronically used by the studied patients with epilepsy as categorized by the ATC classification system. Ten most commonly used medications other than AED(s) included: levothyroxine ( $n = 42$ , 6.3%), metoprolol ( $n = 27$ , 4.1%), simvastatin ( $n = 25$ , 3.8%), acetylsalicylic acid ( $n = 24$ , 3.6%), atorvastatin ( $n = 23$ , 3.6%), amlodipine ( $n = 19$ , 2.9%), perindopril ( $n = 18$ , 2.7%), sertraline ( $n = 17$ , 2.6%), ramipril ( $n = 16$ , 2.4%) and ethinylestradiol (15, 2.3%).

**Table 1**  
General characteristics of studied patients with epilepsy and current treatment of epilepsy (doses reported as median with interquartile range).

| Variable  |                              |
|---|------------------------------|
| Female sex; n (%)   | 395 (59.6%)                  |
| Age (years); median (q1–q3)   | 31 (25–42)                   |
| Age at onset of epilepsy (years); median (q1–q3)                                      | 16 (10–25)                   |
| Epilepsy type; n (%)  |                              |
| Generalized   | 142 (21.4%)                  |
| Focal   | 501 (75.6%)                  |
| Combined (generalized and focal)  | 11 (1.7%)                    |
| Unknown   | 9 (1.3%)                     |
| Frequency of seizures; n (%)  |                              |
| More than 1 per month   | 234 (35.3%)                  |
| 1–12 per year   | 177 (26.7%)                  |
| Less than 1 per year  | 251 (37.9%)                  |
| Number of currently used AEDs; n (%)  |                              |
| 1   | 361 (54.5%)                  |
| 2   | 219 (33.0%)                  |
| 3   | 74 (11.2%)                   |
| 4   | 9 (1.3%)                     |
| The most commonly used AEDs (in mono- or polytherapy); n(%) and its daily dose (mg/d) |                              |
| Valproic acid   | 329 (49.6%) 1500 (1000–2000) |
| Levetiracetam   | 225 (33.9%) 2000 (1000–2500) |
| Lamotrigine   | 148 (22.3%) 250 (200–400)    |
| Carbamazepine   | 130 (19.6%) 800 (600–1200)   |
| Topiramate  | 70 (10.6%) 200 (200–300)     |
| Oxcarbazepine   | 52 (7.8%) 1200 (900–1800)    |

q1–q3 – interquartile range.

**Table 2**  
Number of drugs used chronically by studied patients with epilepsy.

| Number of drugs used chronically | All medications (including AEDs) | Medications for somatic disorders (excluding AEDs) | Medications for psychiatric disorders (excluding AEDs) |
|----------------------------------|----------------------------------|--|--|
| 0                                | 0                                | 444 (67.0%)  | 569 (85.8%)  |
| 1                                | 217 (32.7%)                      | 93 (14.0%)   | 63 (9.5%)  |
| 2                                | 179 (27.0%)                      | 64 (9.7%)  | 19 (2.9%)  |
| 3                                | 139 (21.0%)                      | 31 (4.7%)  | 10 (1.5%)  |
| 4                                | 56 (8.4%)                        | 16 (2.4%)  | 1 (0.15%)  |
| 5                                | 36 (5.4%)                        | 10 (1.5%)  | 1 (0.15%)  |
| 6                                | 18 (2.7%)                        | 4 (0.6%)   |  |
| 7                                | 9 (1.5%)                         | 0  |  |
| 8                                | 4 (0.6%)                         | 1 (0.1%)   |  |
| 9                                | 3 (0.4%)                         |  |  |
| 10                               | 1 (0.15%)                        |  |  |
| 11                               | 1 (0.15%)                        |  |  |

AED – antiepileptic drug.

### 3.3. Interactions between AEDs and other drugs

Among 265 patients who used medications other than AEDs, major interactions between AEDs and non-AEDs were found in 31 patients (11.7%) and moderate interactions were found in further 49 patients (18.4%). Most prevalent major interactions included: ethinylestradiol/estradiol – valproate/oxcarbazepine/carbamazepine (14 pairs), sertraline-carbamazepine (5 pairs), simvastatin-carbamazepine (4 pairs), and olanzapine-carbamazepine (2 pairs). Table 4 provides detailed information about all major and moderate interactions found in studied patients.

Table 5 summarizes differences between patients with and without major or moderate interactions between AED(s) and other drugs. Patients with interactions were less likely to have rare seizures, and more

**Table 3**  
Medications chronically used by the studied patients with epilepsy as categorized by the Anatomical Therapeutic Chemical (ATC) classification system.

| Medications classified according to ATC                                       | N (%) of patients |
|---|-------------------|
| <b>Alimentary tract and metabolism (A)</b>                                    | 36 (5.4%)         |
| Drugs for acid related disorders (A02)  | 23 (3.5%)         |
| Drugs used in diabetes (A10)  | 9 (1.4%)          |
| Vitamins (A11)  | 5 (0.7%)          |
| Other alimentary tract and metabolism products (A16)                          | 7 (1.1%)          |
| <b>Blood and blood forming organs (B)</b>                                     | 34 (5.1%)         |
| Platelet aggregation inhibitors (B01AC)                                       | 24 (3.6%)         |
| Anticoagulants (B01AA or B01AE or B01AF)                                      | 10 (1.5%)         |
| <b>Cardiovascular system (C)</b>  | 111 (16.7%)       |
| Diuretics (C03)   | 21 (3.2%)         |
| Beta-blocking agents (C07)  | 54 (8.1%)         |
| Calcium channel blockers (C08)  | 24 (3.6%)         |
| Agents acting on renin (C09)  | 52 (7.8%)         |
| ACE inhibitors (C09 A)  | 37 (5.6%)         |
| Angiotensin II antagonists (C09C)   | 15 (2.3%)         |
| Lipid modifying agents (C10)  | 52 (7.8%)         |
| <b>Genito-urinary system and sex hormones (G)</b>                             | 33 (5.0%)         |
| Progestogens and estrogens (fixed combinations) (G03AA)                       | 21 (3.2%)         |
| <b>Systemic hormonal preparations excluding sex hormones and insulins (H)</b> | 48 (7.2%)         |
| Corticosteroids for systemic use (H02)  | 5 (0.7%)          |
| Thyroid therapy (H03)   | 44 (6.6%)         |
| <b>Antineoplastic and immunomodulating agents (L)</b>                         | 4 (0.6%)          |
| <b>Musculo-skeletal system (M)</b>  | 4 (0.6%)          |
| <b>Nervous system (N)</b>   | 94 (14.2%)        |
| Antipsychotics (N05 A)  | 35 (5.3%)         |
| Anxiolytics/hypnotics (N05B)  | 26 (3.9%)         |
| Antidepressants (N06 A)   | 62 (9.3%)         |
| <b>R Respiratory system</b>   | 20 (3.0%)         |
| Drugs for obstructive airway diseases (R03)                                   | 20 (3.0%)         |
| <b>V Various</b>  | 14 (2.1%)         |

likely to use carbamazepine or hepatic enzyme-inducing AEDs in general. The median number of currently used medications was also higher in those with interactions.

Independent predictors of occurrence of major or moderate interaction between AED(s) and non-AED(s) were assessed with logistic regression modelling and included total number of currently used medications (odds ratio [OR] = 1.26, 95% confidence interval [CI] = 1.07–1.48 per each additional medication;  $p = 0.005$ ) and the use of hepatic enzyme-inducing AED (OR = 2.78, 95% CI = 1.51–5.12;  $p < 0.001$ ). When the latter variable was replaced with individual AEDs, the use of carbamazepine (OR = 3.44, 95% CI = 1.80–6.52;  $p < 0.001$ ) or oxcarbazepine (OR = 3.34, 95% CI = 1.41–7.90;  $p = 0.005$ ) emerged as independent predictors of significant interactions. The number of currently used AEDs was not an independent predictor of interactions (OR = 1.32 [95% CI = 0.92–1.92],  $p = 0.13$ ).

## 4. Discussion

Our findings highlight the high prevalence of co-medication among non-selected patients with epilepsy and confirm relatively high risk of potential interactions between AEDs and other drugs in this population.

Studied population of patients with epilepsy was comparable to other typical populations of patients with epilepsy - about 75% of patients suffered from focal epilepsy, 54.5% of patients were on monotherapy with AED and four most commonly used AEDs included valproate, levetiracetam, lamotrigine and carbamazepine; these findings are very similar to the most recent study from Germany [16]. Also, phenytoin was used in less than 1% of our population and in patients studied by Willems et al. [16]. This emphasizes much the same pattern of AED prescribing in Europe and contrasts sharply with patterns reported in United States, where phenytoin was rated as most commonly prescribed AED (49% among women and 60% in men) [7]. Such a difference may have significant impact on findings related to drug

**Table 4**

Major and moderate interactions between antiepileptic drugs and other medications in studied patients with epilepsy (major interactions are highlighted in red and moderate interactions – in yellow). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

|                    | TPM | VPA | PB | PHT | CBZ | LTG | OXC | LCZ |
|--------------------|-----|-----|----|-----|-----|-----|-----|-----|
| Acenocumarol       |     |     |    |     | 1   |     |     |     |
| Aspirin            |     | 10  |    |     |     |     |     |     |
| Citalopram         | 1   | 2   |    |     |     |     |     |     |
| Clomipramine       |     | 1   |    |     |     |     |     |     |
| Clorazepate        |     |     |    |     | 1   |     |     |     |
| Clozapine          |     |     | 1  |     | 1   |     |     |     |
| Desmopressin       |     |     |    |     | 1   |     |     |     |
| Escitalopram       |     |     |    |     |     | 2   |     |     |
| Estazolam          |     |     |    | 1   |     |     |     |     |
| Estradiol          |     | 1   |    |     |     |     | 4   |     |
| Ethinylestradiol   |     | 6   |    |     | 1   | 8   | 2   |     |
| Flunarizine        |     |     |    |     | 1   |     |     |     |
| Levothyroxine      |     |     | 1  |     | 10  |     |     |     |
| Metformin          |     |     |    |     |     | 1   |     |     |
| Methylprednisolone |     |     |    |     | 1   |     |     |     |
| Metoclopramide     | 1   |     |    |     |     |     |     |     |
| Mianserin          |     |     |    |     |     |     | 2   |     |
| Nitrendipine       |     |     |    | 1   |     |     |     |     |
| Olanzapine         |     | 2   |    |     | 2   |     |     |     |
| Opiamol            |     |     |    |     |     | 1   |     |     |
| Perazine           |     |     |    |     | 1   |     |     |     |
| Propranolol        |     |     |    |     | 1   |     |     | 1   |
| Ranitidine         |     |     |    |     | 1   |     |     |     |
| Risperidone        | 3   | 4   |    |     | 1   | 3   |     |     |
| Sertraline         |     |     |    |     | 5   | 1   | 2   |     |
| Simvastatin        |     |     |    |     | 4   |     | 2   |     |
| Trazodone          | 1   |     |    |     |     |     |     |     |
| Warfarin           |     | 1   |    |     | 1   |     |     |     |

TPM – topiramate; VPA – valproic acid; PB – phenobarbital; PHT – phenytoin; CBZ – carbamazepine; LTG – lamotrigine; OXC – oxcarbazepine; LCZ – lacosamide.

**Table 5**

Comparison of demographics, characteristics of epilepsy and medications used between patients with and without moderate or major interactions between AEDs and other drugs (patients who took at least one drug other than AED, n = 265).

| Variable   | Patients with significant interactions (n = 80) | Patients without significant interactions (n = 185) | P-value |
|--|---|---|---------|
| Female sex; n (%)                                    | 51 (63.7%)                                      | 112 (60.2%)   | 0.62    |
| Age (years); median (q1–q3)                          | 43 (28–55)                                      | 39.0 (29–54)  | 0.70    |
| Age at onset of epilepsy (years); median (q1–q3)     | 19 (13–42)                                      | 21.5 (12–37)  | 0.92    |
| Epilepsy type; n (%)                                 |   |   |         |
| Generalized  | 9 (11.2%)                                       | 28 (15.0%)  | 0.40    |
| Focal  | 67 (83.8%)                                      | 155 (83.3%)   | 0.99    |
| Combined (generalized and focal)                     | 1 (1.3%)  | 1 (0.5%)  | 0.51    |
| Unknown  | 3 (3.7%)  | 2 (1.1%)  | 0.16    |
| Frequency of seizures;* n (%)                        |   |   |         |
| More than 1 per month                                | 30 (37.5%)                                      | 78 (41.9%)  | 0.48    |
| 1–12 per year  | 31 (38.7%)                                      | 45 (24.2%)  | 0.02    |
| Less than 1 per year                                 | 19 (23.8%)                                      | 65 (33.9%)  | 0.07    |
| Number of currently used AEDs; median (q1–q3)        | 2 (1–2)   | 1 (1–2)   | 0.07    |
| Number of currently used medications; median (q1–q3) | 4 (3–5)   | 3 (2–4)   | 0.001   |
| Current use of:                                      |   |   |         |
| Hepatic enzyme-inducing AED                          | 30 (37.5%)                                      | 31 (16.7%)  | < 0.001 |
| Valproic acid  | 34 (42.5%)                                      | 84 (45.2%)  | 0.66    |
| Lamotrigine  | 19 (23.7%)                                      | 39 (21.0%)  | 0.63    |
| Carbamazepine  | 29 (36.2%)                                      | 31 (16.1%)  | < 0.001 |
| Oxcarbazepine  | 12 (15.0%)                                      | 15 (8.1%)   | 0.09    |
| Phenobarbital  | 2 (2.6%)  | 4 (2.1%)  | 0.58    |
| Phenytoin  | 2 (1.6%)  | 0   | 0.09    |
| Topiramate   | 9 (11.2%)                                       | 18 (9.7%)   | 0.71    |
| Lacosamide   | 1 (1.3%)  | 5 (2.7%)  | 0.67    |

AED – antiepileptic drug; q1–q3 – interquartile range.

interactions, as phenytoin, potent hepatic enzyme-inducer, is commonly involved in interactions between AEDs and other drugs. Scarce use of phenytoin might shift the relative risk of interactions to other, more commonly used AEDs. The study by Gidal et al. [7], which was probably the only one to deal with general population of patients with epilepsy, did not report interactions in individual patients, and focused on co-medication and potential interactions at the level of specific age groups or between sexes. Their population differed also from ours regarding the disproportionately low percentage of patients on monotherapy (12.5–16.4%). Nevertheless, they found statins, calcium antagonists and selective serotonin reuptake inhibitors to be the most commonly used medications potentially involved in interactions.

Our sample consisted of patients of various ages and the median age of 31 suggested that the young people were quite prevalent. This feature is responsible for the relative shift of interactions from those related to drugs used mostly in elderly (i.e. antihypertensives, statins, antithrombotics) towards the most prevalent interactions between AEDs and hormones (mostly ethinylestradiol and estradiol used in hormonal contraception). It also impedes comparisons with previous studies which comprised elderly patients. Bruun et al. [9] studied patients aged at least 65, newly diagnosed with epilepsy, and found major interactions in 32% (one major interaction) and in 31% (two major interactions) of patients treated with carbamazepine. They also noted high percentage of patients with polypharmacy defined as the use of more than 10 drugs (27%), while it was extremely rare in our patients (0.1%), most probably due to the younger age of our patients. Faught et al. [10] analyzed Medicare claims in a random sample of patients with epilepsy older than 66 and found potential interactions affecting efficacy of drugs other than AED in 24.5% of incident cases and in 39% of prevalent cases. As mentioned earlier, the common use of phenytoin in those patients (26.4–40.1% among those exposed to drugs other than AED) may explain the high prevalence of possible interactions. It should be noted that the recent changes in AEDs prescription pattern among US patients with newly diagnosed epilepsy, including rapid decline of phenytoin use as a first AED (6.5% of patients), would most probably result in lesser risk of potential drug interactions [17].

The drug interaction database chosen for this study (Micromedex®) was included in the recent systematic review of such electronic sources [18] and was found to be most often used in studies related to drug interactions. Nevertheless, some differences between databases do exist in terms of definitions and suggested level of interactions which may lead to subsequent differences in reporting of major or moderate interactions. Also, this database is available commercially only and therefore probably not chosen as the primary source among physicians in Poland, which decreases the practical utility of our findings for the local practitioners.

Majkowska-Zwolińska et al. [19] analyzed the use and cost of concomitant medications in a similarly large group of epileptic patients in Poland (n = 772; mean age, 27.4 years). While the most common co-medication classes in their study (drugs for nervous system and for cardiovascular disorders) were also most commonly used in our cohort of patients, the direct comparison is difficult due to different methodological approach. These authors analyzed also medications taken sporadically or acutely, with the resulting conclusion that nearly 2/3 of patients took dietary supplements of vitamins and minerals.

The term ‘medications used to treat psychiatric disorders’ was chosen to describe specific classes of medications. We had no data to verify whether the given drug was prescribed for psychiatric disorder – it can be expected that some medications of that kind could be as well used to treat e.g. neuropathic pain or sleep-related problems.

Limitations of the study include the use of population of tertiary epileptic clinic which may differ substantially from the general population of patients with epilepsy in regard of seizure frequency or use of polytherapy. Also, the awareness of potential interactions might be higher among epileptologists than in case of family physicians. Those factors may theoretically affect the risk of interactions in either

direction (higher risk due to more complex use of AED or lower risk due to the better insight into the potential interactions). The majority of patients with epilepsy in Poland are managed by neurologists rather than family physicians, however, and the cohort of patients in our clinic is by no means limited to patients with refractory epilepsy. As discussed above, the characteristics of the studied group is similar to other studies based on unselected patients with epilepsy. We studied consecutive patients (all patients agreed to participate) and the only exclusion criterion (lack of treatment with AED) was inevitable, as the study dealt with the drug interactions. Also, the analysis involved all medications used chronically, including those not reimbursed by the national health service, and the data of individual patients were used rather the compiled data from health insurance databases.

## 5. Conclusions

Our survey among patients with epilepsy seen in tertiary epilepsy center suggests that the potential major or moderate interactions between AEDs and non-AEDs are still prevalent (30.1% of patients exposed to at least one medication other than AED or 12.1% of the entire cohort of patients with epilepsy), even though the use of AEDs most often related to those interactions (especially phenytoin) is in decline. Epileptologists and other health service providers should be aware of the potential interactions of AEDs with other drugs to limit potential harm and optimize therapeutic efficacy of AEDs.

## Declaration of interest

MB received honoraria for publications from Sanofi-Genzyme; honoraria for lectures, travel expenses and conference fees from Sanofi, Adamed, Teva Pharmaceutical, Neuraxpharm, Glenmark, UCB Pharma.

AS received honoraria for lectures from Bayer, Boehringer Ingelheim, Novartis, Polpharma, Bristol-Myers Squipp, Novartis, Biogen, Teva Pharmaceutical, Medtronic; for the participation in advisory meetings from Bayer, Boehringer Ingelheim, Novartis.

WT received honoraria for publications from Sanofi-Genzyme; honoraria for lectures, travel expenses, and conference fees from Shire and CSL Behring.

AI and ML report no conflict of interest

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## References

- [1] Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs. A 30-year longitudinal cohort study. *JAMA Neurol* 2018;75:279–86.
- [2] Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. *Epileptic Disord* 2014;16:409–32.
- [3] Woroń J, Siwek M. Unwanted effects of psychotropic drug interactions with medicinal products and diet supplements containing plant extracts. *Psychiatr Pol* 2018;52:983–96.
- [4] Bosak M, Cyranka K, Dudek D, Kowalik M, Molek P, Słowik A. Psychiatric comedication in patients with epilepsy. *Epilepsy Behav* 2018;83:207–11.
- [5] Ottman R, Lipton RB, Ettinger AB, Cramer JA, Reed ML, Morrison A, et al. Comorbidities of epilepsy: results from the Epilepsy Comorbidities and Health (EPIC) survey. *Epilepsia* 2011;52:308–15.
- [6] Gaitatzis A, Sisodiya SM, Sander JW. The somatic comorbidity of epilepsy: a weighty but often unrecognized burden. *Epilepsia* 2012;53:1282–93.
- [7] Gidal BE, French JA, Grossman P, Le Teuff G. Assessment of potential drug interactions in patients with epilepsy. Impact of age and sex. *Neurology* 2009;72:419–25.
- [8] Pugh MJ, VanCott AC, Steinman MA, Mortensen EM, Amuan ME, Wang CP, et al. Choice of initial antiepileptic drug for older veterans: possible pharmacokinetic drug interactions with existing medications. *J Am Geriatr Soc* 2010;58:465–71.
- [9] Bruun E, Virta LJ, Kälviäinen R, Keränen T. Co-morbidity and clinically significant interactions between antiepileptic drugs and other drugs in elderly patients with newly diagnosed epilepsy. *Epilepsy Behav* 2017;73:71–6.

- [10] Faught E, Szaflarski JP, Richman J, Funkhouser E, Martin RC, Piper K, et al. Risk of pharmacokinetic interactions between antiepileptic and other drugs in older persons and factors associated with risk. *Epilepsia* 2018;59:715–23.
- [11] Hamer HM, Dodel R, Strzelczyk A, Balzer-Geldsetzer M, Reese JP, Schöffski O, et al. Prevalence, utilization, and costs of antiepileptic drugs for epilepsy in Germany – a nationwide population-based study in children and adults. *J Neurol* 2012;259:2376–84.
- [12] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014;55:475–82.
- [13] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. *Epilepsia* 2017;58:512–21.
- [14] WHO Collaborating Centre for Drug Statistics Methodology. ATC – structure and principles. 2018 Accessed 16 October 2018 [https://www.whocc.no/atc/structure\\_and\\_principles](https://www.whocc.no/atc/structure_and_principles).
- [15] IBM micromedex® drug interaction checking (electronic version). Colorado, USA: IBM Watson Health, Greenwood Village; 2018 Accessed 16 October 2018 <https://www.micromedexsolutions.com>.
- [16] Willems LM, Richter S, Watermann N, Baue S, Klein KM, Reese L, et al. Trends in resource utilization and prescription of anticonvulsants for patients with active epilepsy in Germany from 2003 to 2013 – a ten-year overview. *Epilepsy Behav* 2018;83:28–35.
- [17] Faught E, Helmers S, Thurman D, Kim H, Kalilani L. Patient characteristics and treatment patterns in patients with newly diagnosed epilepsy: a US database analysis. *Epilepsy Behav* 2018;85:37–44.
- [18] Kongsholm GG, Nielse AKT, Damkier P. Drug interaction databases in medical literature: transparency of ownership, funding, classification algorithms, level of documentation, and staff qualifications. A systematic review. *Eur J Clin Pharmacol* 2015;71:1397–402.
- [19] Majkowska-Zwolińska B, Jędrzejczak J, Majkowski J. Use and costs of concomitant medicines in epileptic patients in Poland: a 12-month prospective multicentre study. *Seizure* 2011;20:673–8.