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ORIGINAL RESEARCH ARTICLE

Adverse Event Profiles of Antiseizure Medications and the Impact of Coadministration on Drug Tolerability in Adults with Epilepsy

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Abstract

Background Antiseizure medication (ASM) as monotherapy or in combination is the treatment of choice for most patients with epilepsy. Therefore, knowledge about the typical adverse events (AEs) for ASMs and other coadministered drugs (CDs) is essential for practitioners and patients. Due to frequent polypharmacy, it is often difficult to clinically assess the AE profiles of ASMs and differentiate the influence of CDs.

Objective This retrospective analysis aimed to determine typical AE profiles for ASMs and assess the impact of CDs on AEs in clinical practice.

Methods The Liverpool AE Profile (LAEP) and its domains were used to identify the AE profiles of ASMs based on data from a large German multicenter study (Epi2020). Following established classifications, drugs were grouped according to their mode of action (ASMs) or clinical indication (CDs). Bivariate correlation, multivariate ordinal regression (MORA), and artificial neural network (ANNA) analyses were performed. Bivariate correlation with Fisher's *z*-transformation was used to compare the correlation strength of LAEP with the Hospital Anxiety and Depression Scale (HADS) and Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) to avoid LAEP bias in the context of antidepressant therapy.

Results Data from 486 patients were analyzed. The AE profiles of ASM categories and single ASMs matched those reported in the literature. Synaptic vesicle glycoprotein 2A (SV2A) and voltage-gated sodium channel (VGSC) modulators had favorable AE profiles, while brivaracetam was superior to levetiracetam regarding psychobehavioral AEs. MORA revealed that, in addition to seizure frequency, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) modulators and antidepressants were the only independent predictors of high LAEP values. After Fisher's *z*-transformation, correlations were significantly lower between LAEP and antidepressants than between LAEP and HADS or NDDI-E. Therefore, a bias in the results toward over interpreting the impact of antidepressants on LAEP was presumed. In the ANNA, perampanel, zonisamide, topiramate, and valproic acid were important nodes in the network, while VGSC and SV2A modulators had low relevance for predicting relevant AEs. Similarly, cardiovascular agents, analgesics, and antipsychotics were important CDs in the ANNA model.

Conclusion ASMs have characteristic AE profiles that are highly reproducible and must be considered in therapeutic decision-making. Therapy using perampanel as an AMPA modulator should be considered cautiously due to its relatively high AE profile. Drugs acting via VGSCs and SV2A receptors are significantly better tolerated than other ASM categories or substances (e.g., topiramate, zonisamide, and valproate). Switching to brivaracetam is advisable in patients with psychobehavioral AEs who take levetiracetam. Because CDs frequently pharmacokinetically interact with ASMs, the cumulative AE profile must be considered.

Trial registration DRKS00022024, U1111-1252-5331.

1 Introduction

Despite rapid advances in epilepsy surgery and neuromodulatory procedures over the last decade, oral antiseizure medications (ASMs) remain the gold standard for treating most patients with epilepsy [1–3]. The large number of available ASMs makes the individualized selection of the agents, or

Extended author information available on the last page of the article

Key Points

Adverse event (AE) profiles for antiseizure medications differ between modes of action and between single substances with the same molecular target.

Perampanel is an AMPA receptor antagonist that is associated with an unfavorable AE profile.

Topiramate, valproate, and zonisamide therapy are associated with an unfavorable AE profile.

Brivaracetam produces fewer psychobehavioral AEs than levetiracetam.

Voltage-gated sodium channel(modulators such as dibenzazepines, lamotrigine, and lacosamide have favorable AE profiles.

their combination, by the treating physician indispensable [4, 5]. While national and international guidelines can be used as decision-making aids, the patient's situation and the expected adverse event (AE) profile of the ASM must also be considered [6]. A desire for pregnancy in the short or medium term, the patient's age, specific AE profiles of the ASM, and comorbidities are important factors [7–9]. For example, in patients with depression or bipolar disorder, lamotrigine (LTG), a typical voltage-gated sodium channel (VGSC) modulator, is preferred because of its synergistic mood-stabilizing effects, whereas the synaptic vesicle glycoprotein 2A (SV2A) modulators levetiracetam (LEV) and (to a lesser extent) brivaracetam (BRV) may trigger or exacerbate psychobehavioral AEs [10–12]. Treatment with the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor modulator perampanel (PER) is associated with an increased risk of psychosis [13]. Other ASMs, such as valproic acid (VPA) and topiramate (TPM), have been associated with a handicapping tremor and psychomotor retardation, respectively [14, 15]. In addition to these common examples, other less common AEs must be expected, especially in patients taking several ASMs or other drugs [16]. According to the literature, approximately 30% of patients with epilepsy are treated with potentially highly interactional combinations of ASMs, or ASMs and other coadministered drugs (CDs), which complicate the assessment of clinical AE profiles [17, 18]. Dramatic increases and decreases in ASM serum levels have been described, especially in patients with polypharmacy, which lead to intoxication, subtherapeutic levels, and even renal or liver failure [19–25].

This study aimed to determine the AE profiles of ASMs and analyze the impact of CDs on AE profiles in clinical practice based on data from a large, German, multicenter analysis.

2 Methods

2.1 Patients and Study Design

This analysis was part of the Epi2020 study, a prospective German multicenter study conducted between October and December 2020 that enrolled adult patients with confirmed epilepsy diagnosis at four epilepsy centers in Frankfurt am Main, Greifswald, Marburg, and Münster. The Epi2020 study was a large-scale study aiming to assess the medical care and other aspects [e.g., quality of life (QOL), depression, and telemedicine] of patients with epilepsy [26–30]. The evaluation of the AE spectrum presented here was a secondary outcome measure of the Epi2020 study, and it was not included in the study power calculation. All study centers offer specialized, interdisciplinary inpatient and outpatient care for patients with epilepsy, epileptic encephalopathies, or epilepsy-associated syndromes.

All adult patients (aged ≥ 18 years) with a confirmed diagnosis of epilepsy were eligible for inclusion after providing written informed consent at one of the study centers. Patients with a questionable or doubtful diagnosis were not enrolled. Patients were asked to complete a comprehensive paper-based questionnaire that included epilepsy-specific, medical, utility, and sociodemographic questions and scores established in previous studies [27, 31, 32]. Based on the design of the questionnaire, it was not possible to distinguish between short-term AEs during uptitration and AEs associated with the long-term use of ASMs or CDs. All information provided by the patients was voluntary. Post hoc confirmation of the accuracy and completeness of the information was not feasible due to the study design.

To improve the evaluation and validity of the statements and to minimize potential biases, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) statements were followed [33, 34]. The Epi2020 study and further analyses of its collected data were approved by the local ethics committee at Goethe University prior to enrollment (reference: 19-440). The Epi2020 study was registered with the German Clinical Trials Register (DRKS00022024; Universal Trial Number: U1111-1252-5331).

2.2 Scores and Metrics

2.2.1 Liverpool Adverse Events Profile

This analysis used the well-established and validated Liverpool Adverse Events Profile (LAEP) to measure ASM

tolerability in clinical practice [35–38]. The LAEP is a self-reported scale comprising 19 items rated on a four-point Likert scale. The resulting total score ranges from 19 to 76, with a higher score indicating more frequent symptoms. The total LAEP score and the scores for its subdomains were mostly used descriptively. For the neuronal network-based analysis, LAEP was binary coded on the basis of a total score cut-off of 37 to distinguish clinically relevant (total score ≥ 37) and irrelevant (total score < 37) AE profiles [39].

2.2.2 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) was used to assess depressive symptoms. The HADS is a self-reported scale containing 14 items rated on a four-point Likert scale from 0 to 3. The items each comprise seven questions relating to anxiety and depression, resulting in a total score of 0 to 21 for each criterion [40].

2.2.3 Neurological Disorders Depression Inventory for Epilepsy

The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) was used to assess depressive symptoms. The NDDI-E is a self-reported scale containing six items rated on a four-point Likert scale from 1 to 4, resulting in a total score of 0 to 24. A total score ≥ 14 has been identified as a marker of clinically relevant depressive symptoms [41].

2.3 Categorization of Antiseizure Medications and Coadministered Drugs

To facilitate statistical analysis and comply with statistical recommendations on the minimum and maximum feasible number of variables in multivariate regression analysis, ASMs and CDs were divided into categories [42]. Based on an existing classification, the ASMs were categorized according to their primary mechanism of action [43, 44], although this may not reflect all the pharmacological properties of each ASM. This process resulted in the following ASM categories: VGSC modulators [carbamazepine (CBZ), eslicarbazepine (ESL), lacosamide (LCM), LTG, oxcarbazepine (OXC), phenytoin (PHT)], SV2A modulators (BRV, LEV), AMPA modulators (PER), gamma-aminobutyric acid (GABA) modulators [gabapentin (GBP), lorazepam (LZP), phenobarbital (PB), pregabalin (PGB), primidone (PRM)], and other drugs [cannabidiol (CBD), cenobamate (CNB), ethosuximide (ESM), TPM, VPA, zonisamide (ZNS)]. For the categorization of CDs, the well-established USP Therapeutic Categories Model Guidelines published by the US Food and Drug Administration were used [45]. To meet the specifications of the Local Ethics Committee and prevent post hoc identification of individual patients based on the processed data, no LAEP values are reported for drugs taken by two or fewer patients.

2.4 Statistical Analysis

2.4.1 General Aspects and Descriptive Statistics

Statistical analyses were performed using SPSS Statistics 28 (IBM Corporation, Armonk, NY, US). Descriptive data analyses are reported as appropriate for the individual variables as number (percent) or mean ± standard deviation (SD; median, minimum–maximum). Following univariate and multivariate analysis, p values < 0.05 were considered statistically significant. Due to the multivariate and neural network-based analyses used in addition to the descriptive bivariate correlations, no post hoc correction for multiple testing was performed. Figures were created using Prism 9 (GraphPad Software. Inc., CA, US) and Pixelmator Pro (Pixelmator Team, Vilnius, LTU) software.

2.4.2 Bivariate Correlation Analysis

Pearson's bivariate correlation coefficient (r) was used to assess correlations between ASM mono and dual therapies and AE profiles measured by the LAEP and its domains. Pearson's r was visualized as a heatmap to assess the positive correlations between ASMs and LAEPs [46]. All negative values were coded on the basis of the color of the minimum value as there were no positive correlations between ASMs and AE profiles. Except for VGSC modulators, combinations within the same ASM category are uncommon and were not observed in the studied population; therefore, these fields are marked with a white "X", while other unreported combinations are greyed out. Similarly, the correlation between LAEPs and the use of certain ASM categories was assessed independently of the therapeutic regimen and administered CDs. Due to their frequent clinical use, correlations between ASMs and LAEPs for the most common agents in the VGSC [e.g., LTG versus LCM or dibenzazepines (DBZ), such as CBZ, ESL, and OXC] and SV2A (LEV versus BRV) modulator categories were assessed separately. Bivariate correlation analysis was used to assess the impact of depressive symptoms on associations between LAEPs and antidepressant use, using Fischer's z-transformation for statistical comparisons between ASM, LAEP, NDDI-E, and HADS correlation coefficients [47].

2.4.3 Multivariate Ordinal Regression Analysis

Due to the ordinal level of the LAEP and binary dummy coding of ASM variables, only a multivariate ordinal regression analysis (MORA) was feasible [48]. Regardless of the number of ASMs or CDs they took, all patients were

included in the MORA to produce a robust statistical model. To avoid model bias due to the severity of epilepsy or cumulative effects of ASMs and CDs, the model included seizure frequency (ordinal coded: in remission, occasional seizures, or frequent seizures) and the number of ASMs and CDs. These analyses are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

2.4.4 Neuronal Network Analysis

Artificial neural network analysis (ANNA) was performed using the built-in multilayer perceptron model in SPSS Statistics 28. Neural networks use non-linear data modeling to analyze relationships and can improve the output of data analysis, especially in large and complex datasets [49]. To enable ANNA to detect non-linear correlations, a model with one input, one output, and two hidden interlayers was used [50]. The normalized importance of variables within the neural network was used as the output parameter. This calculated value can range from 0.0 (no relevance) to 1.0 (high relevance) and can be specified between 0% and 100% [51]. In the present analysis, ANNA was based on a binary-coded LAEP as the dependent variable, and ASM and CD categories were used as independent variables. Based on a previous study, a total score cut-off of 37 was used to distinguish relevant (total score ≥ 37) from irrelevant (total score < 37) AE profiles [39]. The neural network was trained on 70% of the data (random selection of variables) and evaluated on the remaining 30% of the data.

3 Results

3.1 Study Population, Scores, and Metrics

Four hundred eighty-six patients with a balanced sex distribution (58.2% female versus 41.8% male) and a mean age of 40.5 ± 15.5 years (median 38, range 18–83 years) were analyzed. Four hundred sixty-four (95%) patients reported regularly taking ASMs, with a mean of 1.8 ± 1.0 ASMs (median 2.0, range 0–6); of these patients, 142 (30.3%) reported taking at least one CD, with a mean of 0.8 ± 1.7 CDs (median 0.0, range 0–9). Focal and generalized epilepsy were diagnosed in 329 (67%) and 103 (21.2%) patients, respectively, while the epilepsy syndrome was unclear in 54 (11.1%) patients. Two hundred twelve (43.6%) patients reported ongoing frequent seizures, 79 (16.3%) reported occasional seizures, and 195 (40.1%) reported being seizure-free for ≥ 12 months.

The proportions of complete and usable responses for LAEP, HADS, and NDDI-E were 98.8%, 96.9%, and 95.1%, respectively. The general LAEP, HADS, and NDDI-E characteristics of the study population are shown in Supplementary Table 1.

3.2 Bivariate Correlation Analysis Between LAEPs and ASMs in Mono and Dual Therapy

The bivariate correlations between LAEPs and ASMs are shown as separate heatmaps for mono (Fig. 1a) and dual (Fig. 1b) therapies. Correlations between ASM therapies and total LAEP scores or individual LAEP subdomain scores are presented in Fig. 2a.

Detailed correlation analyses highlighting the AE profiles of individual drugs were performed for frequently used ASMs (i.e., SV2A and VGSC modulators). While there were no relevant correlations between total LAEP scores and DBZ, LTG, or LCM, which are the most relevant VGSC modulators, further analysis of LAEP subdomain scores indicated differences between these ASMs. DBZ use significantly correlated with memory problems, while LTG use correlated with skin problems and impaired concentration. There were no significant correlations between LCM use and any of the LAEP subdomains (Fig. 2b). Regarding SV2A modulators, LEV use correlated with increased AE profiles in many LAEP subdomains, especially those reflecting psychobehavioral symptoms (e.g., aggression, nervousness, and depression). In contrast, BRV had a generally well-tolerated AE profile (Fig. 2c).

3.3 Multivariate Analysis

MORA resulted in a significantly superior model for predicting LAEP ($p < 0.001$) compared with univariate analysis. The following independent variables remained significant in this model: AMPA receptor modulators ($p = 0.044$, OR 2.04, 95% CI 1.07–4.20), antidepressants ($p = 0.004$, OR 2.70, 95% CI 1.38–5.31), and seizure frequency ($p = 0.005$, OR 1.31, 95% CI 1.09–1.57). All other parameters failed to achieve significance. The results of this analysis are presented as a forest plot in Fig. 3.

3.4 Correlation Analysis for LAEP and Depression

There were significant correlations between LAEP and reported antidepressant use ($r = 0.024$, $p < 0.001$), total NDDI-E score ($r = 0.618$, $p < 0.001$), and total HADS score ($r = 0.590$, $p < 0.001$). Fisher's z-transformation of individual coefficients resulted in significantly stronger correlations between LAEP and NDDI-E ($z = -10.776$, $p < 0.001$) and HADS ($z = -10.095$, $p < 0.001$) than between LAEP and antidepressant use, indicating a significantly stronger correlation between LAEP and depressive symptoms than between LAEP and antidepressant therapy. There was no

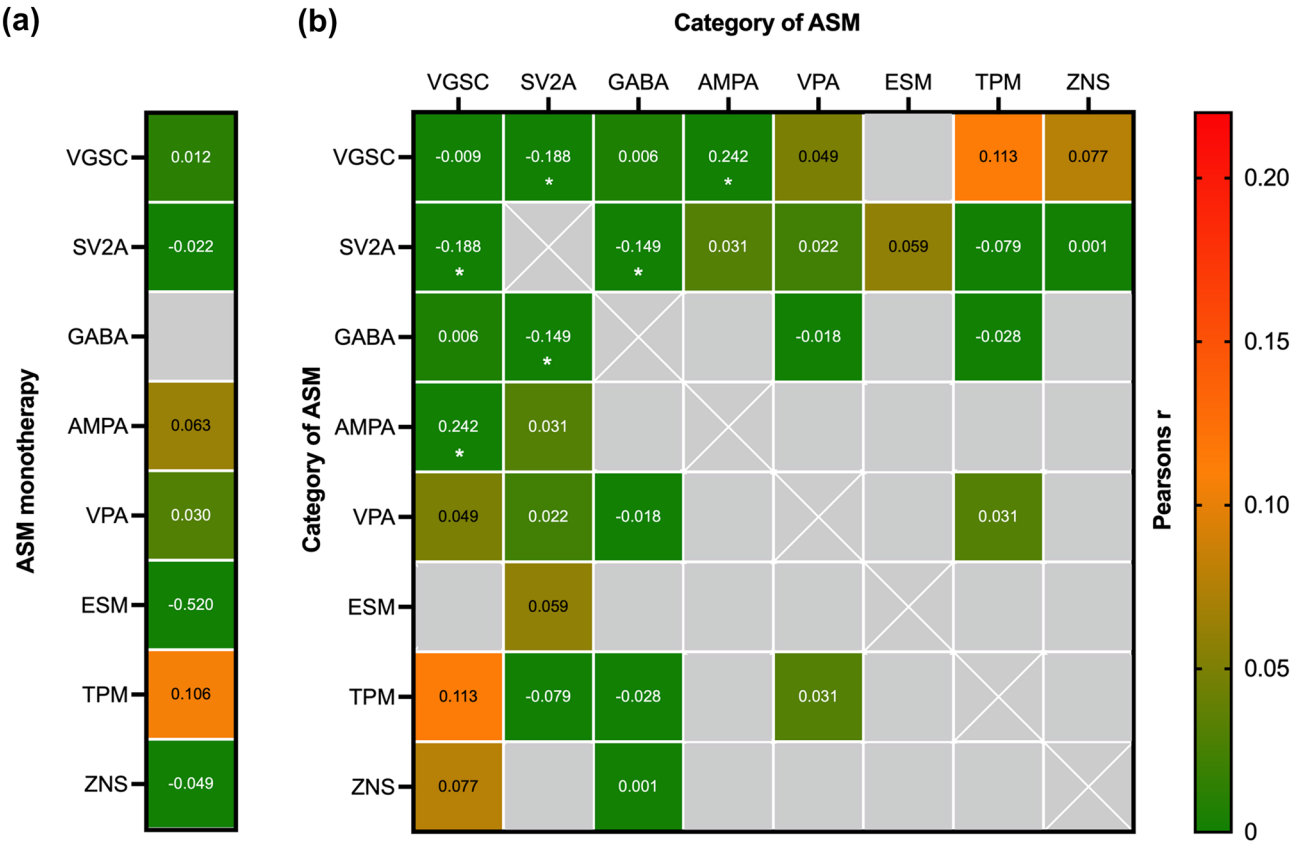

Fig. 1 Tolerability of ASMs as mono and dual therapies: the tolerability of ASM categories measured by the Liverpool Adverse Events Profile (LAEP) in **a** mono and **b** dual therapies is shown based on Pearson's *r* for bivariate correlations with total LAEP scores (for color coding of the correlation coefficient, see bar chart on the right). Significant correlations are highlighted with an asterisk. Missing values are displayed in gray, and unusual combinations of ASMs of the same category are crossed out. *ASM* antiseizure medication, *VGSC* voltage-gated sodium channel, *SV2A* synaptic vesicle glycoprotein 2A, *GABA* gamma-aminobutyric acid, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *VPA* valproic acid, *ESM* ethosuximide, *TPM* topiramate, *ZNS* zonisamide

correlation between ASM use and relevant depressive symptoms. The number of ASMs correlated with depressive symptoms based on NDDI-E ($r = 0.168$, $p < 0.001$) but not HADS ($r = 0.030$, $p = 0.512$).

3.4.1 Neuronal Network Analysis

During training, the neural network correctly predicted an irrelevant AE profile in 42.5% of cases and a relevant AE profile in 72.2% of cases, leading to the correct assignment of AE profiles in 58.9% of cases. During the test phase, the neural network correctly predicted an irrelevant AE profile in 40.3% of cases and a relevant AE profile in 64.4% of cases, leading to the correct assignment of AE profiles in 53.9% of cases. The normalized importance of the single drug nodes for ASMs were 0.13, 0.23, 0.15, 0.43, 0.54, 0.81, and 0.60 for VGSC, GABA, SV2A, AMPA, VPA, TPM, and ZNS, respectively. For CDs, the normalized importance was 0.58 for analgesics, 0.99 for antidepressants, 0.26 for anticoagulants, 0.48 for cardiovascular agents, 0.24 for nutrients/minerals, 0.46 for antipsychotics, and 0.39 for hormones. The normalized importance values within the neuronal network are presented as percentages in separate polar plots for ASMs (Fig. 4a) and CDs (Fig. 4b).

4 Discussion

This retrospective analysis aimed to determine the typical AE profiles of ASMs and assess the impact of CDs on tolerability based on real-life data from 486 adult patients with epilepsy from a prospective German multicenter study (Epi2020) using MORA, ANNA, and bivariate correlation analyses.

In line with the MORA results emphasizing PER as an ASM with an unfavorable AE profile (Fig. 3) and the results of the descriptive analysis (Fig. 2a), several publications highlight psychobehavioral symptoms in addition to dizziness, unsteadiness, and concentration problems as frequently reported AEs and reasons for therapy discontinuation [11,

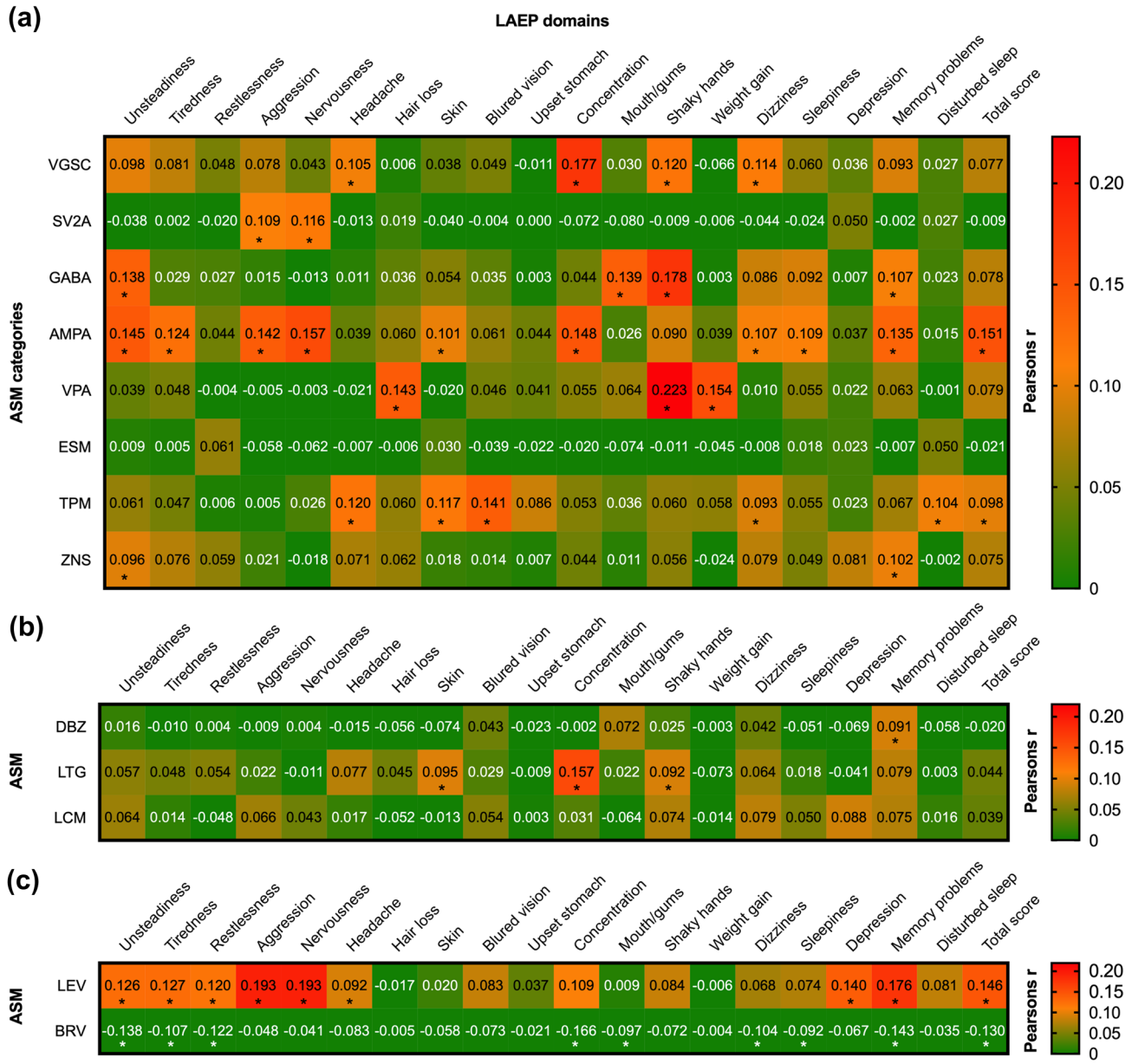

Fig. 2 AE profiles of ASMs: **a** the individual AE profiles of different ASM categories measured by the Liverpool Adverse Events Profile (LAEP) are shown as a heatmap of Pearson's *r* values for bivariate correlations with LAEP total and subdomain scores (for color coding of the correlation coefficient, see bar chart on the right). Individual AE profiles are shown for the frequently used ASM categories: **b** VGSC and **c** SV2A modulators. CBZ, OXC, and ESL are collectively referred to as DBZs. Significant correlations are highlighted with an asterisk. *ASM* antiseizure medication, *VGSC* voltage-gated sodium channel, *SV2A* synaptic vesicle glycoprotein 2A, *GABA* gamma-aminobutyric acid, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *VPA* valproic acid, *ESM* ethosuximide, *TPM* topiramate, *ZNS* zonisamide, *DBZ* dibenzazepine, *LTG* lamotrigine, *LCM* lacosamide, *LEV* levetiracetam, *BRV* brivaracetam

52–58]. Analogous to other ASMs, the occurrence and severity of AEs associated with PER appear to be dose-dependent [59]. The mean and median PER dose in the present study population was 8 mg daily, which is a relatively high titrated dosage, especially compared with dose-finding and registration studies, which may have led to an overrepresentation of AEs [60]. PER, high seizure frequency, and regular antidepressant use were the only other significant predictors according to MORA (Fig. 3). An association between seizure frequency and high LAEP scores has been described previously and has been interpreted as overlap with a decreased health-related and general QOL in patients with epilepsy [35, 39, 61]. The significant contribution of a concomitant medication with antidepressants appears to be

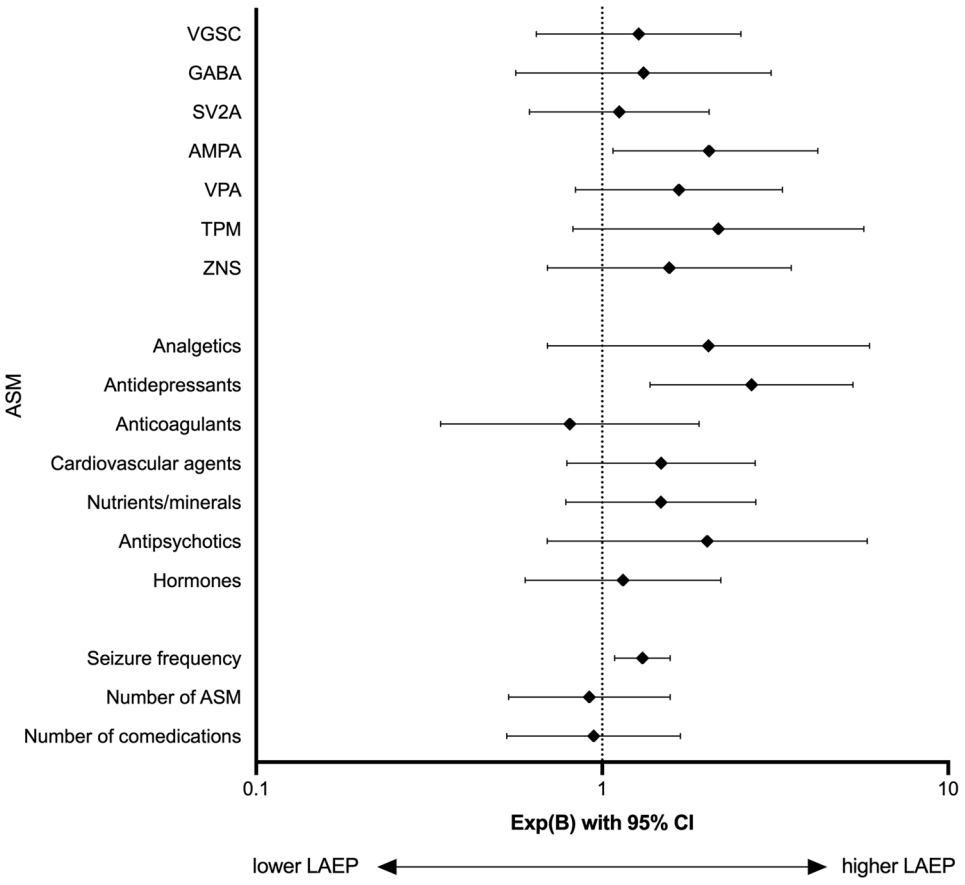

Fig. 3 MORA: A forest plot of the multivariate analysis results identifying independent predictors for increased AE profiles. In addition to seizure frequency as a clinical epilepsy severity marker, only AMPA receptor modulators and antidepressant therapies remained statistically relevant predictors. *ASM* antiseizure medication, *VGSC* voltage-gated sodium channel, *SV2A* synaptic vesicle glycoprotein 2A, *GABA* gamma-aminobutyric acid, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *VPA* valproic acid, *ESM* ethosuximide, *TPM* topiramate, *ZNS* zonisamide, *CI* confidence interval, *LAEP* Liverpool Adverse Events Profile

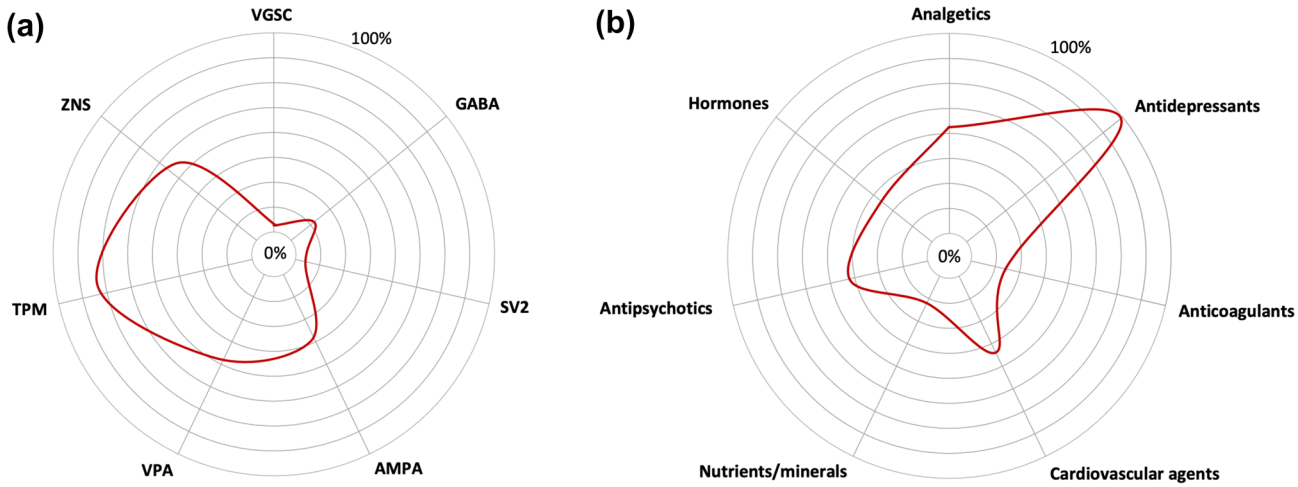

Fig. 4 ANNA: concentric polar plots of the normalized importance of nodes within the ANNA network for **a** ASM categories, comparing relevant AE profiles for VGSC and SV2A modulators to ZNS, TPM, VPA, and AMPA modulators, and **b** CD categories. *ASM* antiseizure medication, *VGSC* voltage-gated sodium channel, *SV2A* synaptic vesicle glycoprotein 2A, *GABA* gamma-aminobutyric acid, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *VPA* valproic acid, *TPM* topiramate, *ZNS* zonisamide

biased by an overlap with reduced QOL due to comorbid depression or increased depressive symptoms [62, 63]. This assumption is confirmed by the significantly higher correlation between LAEP and clinical presentation of relevant depressive symptoms (NDDI-E and HADS) compared with the correlation between LAEP and antidepressant use based on Fisher's *z*-transformation. In contrast with other studies on this topic that report relevant interactions in up to 30%

of cases [17, 18, 64], there were no indications of a relevant potentiation of the AE spectrum or the tolerability of ASMs by CDs detected in this study, which is partly attributable to the limited number of participants and other methodological aspects in the present study. Incompatible drug combinations can lead to relevant interactions, even when drugs are taken for only a short time, as described most recently in the context of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic for combinations of antivirals and ASMs [65, 66]. For example, whether, and to what extent, online interaction databases or apps could represent an approach to improve the detection of interactions requires further investigation, even if limited evidence suggests a potential benefit [17].

Based on the recently published results of the SANAD 2 study, VPA is currently the most recommendable choice for patients with generalized or unclassified epilepsy and is also commonly used in patients with focal epilepsy, namely men, while it is avoided in women of childbearing age due to its proven teratogenic effects [67, 68]. While VPA was not associated with increased LAEP in MORA (Fig. 3), ANNA revealed its relevant importance within the network (Fig. 4), which mirrors the often moderate tolerability of VPA in clinical practice, mainly due to hair loss, tremor, and weight gain (Fig. 2b) [14, 69].

Interestingly, several other ASMs commonly associated with relevant AE profiles (e.g., TPM and ZNS [70, 71]) did not reach significance within the MORA (Fig. 3) but were important variables for LAEP prediction in the ANNA (Fig. 4), which indicates a potential non-linear relationship between the variables within the model. However, this could also be due to the small number of patients receiving TPM or ZNS therapy in the study population. In line with the present findings of LAEP subdomains, impaired vision and dizziness have been described for TPM (Fig. 2b) [72, 73]. While there is some published evidence, the significant positive correlation between TPM use and the LAEP subdomains of headaches, skin problems, and disturbed sleep in the present analysis was clinically unapparent [74–78]. Unsteadiness and memory problems have also been described with ZNS use [79], which is in line with the results of the LAEP subdomain analysis (Fig. 2b).

Analogous to ZNS and TPM, GABA modulators in MORA (Fig. 3) were not predictive factors for poor ASM tolerability, but were relevant factors in ANNA (Fig. 4). Here, the significant positive correlations for unsteadiness, shaky hands, mouth problems, and memory problems (Fig. 2b) appear reasonable, as comparable effects have been described for the most important agents in this class: PGB, GBP, and PRM [80, 81]. Several GABA modulators are approved for epilepsy and the treatment of different tremor etiologies (e.g., PRM for essential tremor, and GBP for orthostatic tremor). In this context, their correlations with shaky hands are more attributable to a synergistic therapeutic use in patients with essential or other types of tremors than to an additional AE [82]. The validity of this study regarding the effects of GABA modulators on AE profiles is limited by the low number of patients treated with these drugs (Tables 1, 2), the analysis of AEs of benzodiazepines is complicated by the fact that they are often used as emergency medications when required 83.

In line with other publications, monotherapy or combination therapy with VGSC and SV2A modulators was well tolerated, according to MORA (Fig. 3) and ANNA (Fig. 4) [71, 84], 85. Nevertheless, both substance groups have different AE profiles that need to be considered when making a treatment decision [71], and these differences are reflected in the descriptive analysis of the LAEP subdomains (Fig. 2a–c). In line with numerous publications on the compatibility of SV2A modulators, LEV and BRV had significant differences in their AE spectra; BRV use was associated with significantly fewer psychobehavioral AEs than LEV (Fig. 2c) [86–90]. These findings highlight the benefit of a possible switch from LEV to BRV in case of psychobehavioral side effects, which is relatively easy without overlapping intake [91]. Despite a generally good AE profile, substance-specific differences are evident regarding the more frequently used VGSC modulators, LTG and LCM, and CBZ, ESL, and OXC as representative dibenzazepines (DBZ, Fig. 2a, b). Regarding VGSC modulators, significant correlations were found with the LAEP subdomains of concentration, shaky hands, and dizziness (Fig. 2a). Here, the mentioned AEs on concentration and shaky hands were attributable to LTG therapy (Fig. 2b) as common drug-specific AEs [92, 93], while memory problems were associated with DBZ therapy (Fig. 2b) [94]. A reliable statement on the AE profile of phenytoin was not possible due to the limited number of cases.

Like all retrospective data analyses, this study and its conclusions are subject to certain limitations and potential biases, most of which are due to the study design. Despite the multicenter approach, a local or national influence on the prevalence and perceptions of AEs is possible, although unlikely, according to the literature [95]. The impact of other stressful factors on the subjective perception of AEs cannot be excluded. For example, the SARS-CoV-2 pandemic was ongoing at the time of data collection, and it had secondary impacts on the care of chronically ill patients [26, 96]. Despite using the LAEP as an established metric, recording AEs through a questionnaire is associated with the risk of under reporting or incorrect reporting of AEs by the patients or their caregivers [97]. The questionnaire used for this study did not allow an estimation of the duration of ASM intake; therefore, no distinction could be made between short-term AEs during uptitration and AEs during long-term, chronic use. For the same reason, we could not analyze whether dose reduction would have led to an improvement or whether the

Table 1 LAEP scores of different ASM categories

	ASM			LAEP score			
	Frequency		Dose (mg)				
	%	*n*	Median	Mean	SD	Median	Range
VGSC blockers	67.9	362	–	38.8	12.2	38.5	19.0–72.0
CBZ	5.3	26	800	38.6	12.1	39.0	22.0–66.0
OXC	7.4	36	1500	37.2	10.8	37.0	19.0–59.0
ESL	1.4	7	1600	36.1	13.6	34.0	23.0–61.0
LTG	39.9	194	300	38.8	12.3	38.0	19.0–72.0
LCM	19.8	96	400	39.1	12.1	40.5	19.0–67.0
SV2A antagonists	50.2	244	–	38.1	12.5	38.0	19.0–72.0
LEV	31.7	154	2000	41.9	11.7	44.0	19.0–72.0
BRV	18.5	90	250	35.9	12.5	34.0	19.0–72.0
AMPA modulator	12.6	61	–	43.0	11.4	44.0	21.0–69.0
PER	12.6	61	8	43.0	11.4	44.0	21.0–69.0
GABA modulator[a]	7.6	29	–	41.5	13.4	42.0	19.0–69.0
PB	1.0	5	100	44.4	15.3	44.0	26.0–66.0
PRM	1.4	7	500	35.1	16.4	31.0	19.0–62.0
GBP	0.6	3	1800	45.0	22.9	54.0	19.0–62.0
PGB	2.1	10	200	43.9	13.2	45.5	28.0–67.0
LZP	0.8	4	2.5	56.8	13.5	58.5	41.0–69.0
Other, unknown[b]	26.5	152	–	40.8	12.8	14.0	19.0–69.0
VPA	15.2	74	1200	40.4	12.9	40.5	19.0–68.0
ESM	1.0	5	500	36.0	12.6	35.5	19.0–51.0
TPM	5.3	26	200	43.2	14.7	41.0	19.0–69.0
ZNS	7.2	35	300	41.4	11.9	42.0	20.0–67.0
CNB	1.2	6	106	40.0	11.0	40.0	26.0–54.0
CBD	1.0	5	400	54.3	14.1	52.0	41.0–72.0
ASM monotherapy	%	*n*		Mean	SD	Median	Range
VGSC	20.2	98	–	36.0	11.9	35.0	19.0–72.0
SV2A	14.0	68	–	35.5	11.1	33.0	19.0–72.0
VPA	3.7	18	–	36.9	11.4	37.0	19.0–54.0
TPM	1.2	6	–	42.7	11.4	43.0	22.0–64.0
AMPA	0.6	3	–	41.7	11.6	43.0	35.0–47.0
ESM	0.4	2	–	30.0	11.5	30.0	19.0–41.0
ZNS	0.2	1	–	28.0	11.6	28.0	28.0–28.0
ASM dual therapy	%	*n*		Mean	SD	Median	Range
VGS + SV2A	17.9	87	–	36.2	12.3	35.0	19.0–72.0
SV2A + VPA	2.9	14	–	39.4	14.3	40.0	20.0–61.0
VGSC + AMPA	2.5	12	–	49.4	10.6	50.0	32.0–64.0
VGSC + VGSC	2.5	12	–	38.1	10.7	37.5	24.0–58.0
VGSC + VPA	1.6	8	–	41.3	13.3	40.5	22.0–63.0
VGSC + GABA	1.4	7	–	38.9	10.1	35.0	26.0–54.0
VGSC + ZNS	1.4	7	–	43.1	12.5	46.0	26.0–58.0
VGSC + TPM	1.2	6	–	45.8	12.4	45.5	28.0–59.0
SV2A + ZNS	1.0	5	–	38.6	8.1	42.0	25.0–46.0
AMPA + SV2A	0.8	4	–	41.0	10.5	39.0	32.0–54.0
GABA + VPA	0.4	2	–	36.5	7.8	36.5	31.0–42.0
SV2A + TPM	0.4	2	–	29.5	14.8	29.5	19.0–40.0

Table 1 (continued)

ASM dual therapy	%	*n*		Mean	SD	Median	Range
TPM + VPA	0.4	2	–	42.0	12.7	42.0	33.0–51.0
VGCC + SV2A	0.2	1	–	48.0	–	48.0	48.0–48.0
GABA + SV2A	0.4	2	–	21.5	3.5	21.5	19.0–24.0
GABA + TPM	0.2	1	–	34.0	–	34.0	34.0–34.0

Classification modified from [43, 44]. ASM categories are presented in descending order of prescription frequency. Only ASMs used in more than two patients are shown to avoid assignability between LAEP values and individual patients

VGSC voltage-gated sodium channel, *SV2A* synaptic vesicle glycoprotein 2A, *GABA* gamma-aminobutyric acid, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *CBZ* oxcarbazepine, ESL eslicarbazepine, *LTG* lamotrigine, *LCM* lacosamide, *LEV* levetiracetam, *BRV* brivaracetam, *PB* phenobarbital, *PRM* primidone, *GBP* gabapentin, *PGB* pregabalin, *LZP* lorazepam, *PER* perampanel, *VPA* valproic acid *ESM* ethosuximide, *TPM* topiramate, *ZNS* zonisamide, *CBD* cannabidiol, *CNB* cenobamate

[a]Not displayed: tiagabine, vigabatrin, lorazepam, clonazepam, clobazam, and midazolam

[b]Not displayed: potassium bromide

[c]Calculated per total number of patients

AEs influenced therapy discontinuation. Correlations of CDs and ASMs with LAEP may be biased due to confounding by low QOL or comorbid depression [35, 98]. In addition, the different prescription preferences of ASMs may have biased the present results, especially regarding drugs, like PER, that are mostly used in complex polytherapy and in patients with more severe and drug-refractory epilepsies. The STROBE and RECORD statements were closely followed to improve the evaluation and validity of the statements and minimize potential biases [33, 34]. Given the limited number of patients, the results of this study can only provide an indication of the tolerability of ASM and CDs. Larger studies are needed to verify the results, especially regarding less frequently prescribed drugs.

Table 2 Coadministered drugs

Drug category	%	*n*
Cardiovascular agents	11.9	58
Nutrients and minerals	10.5	51
Hormones	8.2	40
Antidepressants	7.8	38
Anticoagulants	4.3	21
Gastrointestinal agents	3.1	15
Analgetic agents	2.9	14
Antipsychotics	2.7	13
BGL regulators	1.9	9
Genitourinary agents	1.9	9
MDB agents	1.4	7
OTC agents	1.2	6
Respiratory agents	1.0	5
Anti-inflammatory agents	0.6	3
Anti-gout agents	0.4	2
Ophthalmic agents	0.4	2
Antineoplastics	0.4	2
Immunosuppressive agents	0.4	2
Sedatives and hypnotics	0.2	1
Anti-Parkinson agents	0.2	1
Not classified	0.2	1

Classification modified after [45]. Presentation in descending order of prescription frequency of CD categories

BGL blood glucose level, *MDB* mineral bone density, *OTC* over-the-counter

5 Conclusions

ASMs have characteristic AE profiles that are highly reproducible and should be considered during therapeutic decision-making. Therapy with PER, which is the only currently available AMPA antagonist, should be considered carefully due to significantly more frequently reported AEs, especially in the nonspecific and psychobehavioral subdomains, compared with other ASMs. Drugs acting via VGSCs and SV2A receptors are significantly better tolerated than other ASM categories or agents (e.g., TPM, ZNS, and VPA). However, decision-making tools and guidance would be helpful in individual cases [99, 100]. As CDs frequently pharmacokinetically interact with ASMs, attention must be given to the cumulative AE profile.

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Ethics approval This study was approved by the Ethics Advisory Board of Goethe University (Frankfurt am Main, Germany) before its conduction (reference number 19-440).

Consent to participate Study participation was voluntary. Subjects were only enrolled after written informed consent had been obtained.

Consent for publication Not applicable.

Availability of data and material The datasets generated and/or analyzed during this study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Authors' contributions A. Strzelczyk conceived the idea for the initial trial and was responsible for the survey. L.M. Willems developed the idea for this analysis. F. von Podewils, S. Knake, S. Kovac, J. P. Zöllner, F. Rosenow and A. Strzelczyk collected the data. M. van den Goten and L.M. Willems processed the data and performed the statistical analyses. L. M. Willems, M. van den Goten, J.P. Zöllner, and A. Strzelczyk drafted the initial manuscript. All authors wrote, edited, and significantly contributed to the final manuscript. All authors approved the final manuscript for submission.

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