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Psychiatric and behavioral side effects of antiepileptic drugs in adults with epilepsy

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ABSTRACT

Purpose: Psychiatric and behavioral side effects (PBSEs) are common, undesirable effects associated with antiepileptic drug (AED) use. The objective of the study was to compare the PBSE profiles of older and newer AEDs in a large specialty practice-based sample of patients diagnosed with epilepsy.
Methods: As part of the Columbia and Yale AED Database Project, we reviewed patient records including demographics, medical history, AED use, and side effects for 4085 adult patients (age: 18 years) newly started on an AED regimen. Psychiatric and behavioral side effects were determined by patient or physician report in the medical record, which included depressive mood, psychosis, anxiety, suicidal thoughts, irritability, aggression, and tantrum. Significant non-AED predictors of PBSE rate were first determined from 83 variables using logistic regression. Predictors were then controlled for in the comparison analysis of the rate of PBSEs and intolerable PBSEs (PBSEs that led to dosage reduction or discontinuation) between 18 AEDs.
Results: Psychiatric and behavioral side effects occurred in 17.2% of patients and led to intolerability in 13.8% of patients. History of psychiatric condition(s), secondary generalized seizures, absence seizures, and intractable epilepsy were associated with increased incidence of PBSE. Levetiracetam (LEV) had the greatest PBSE rate (22.1%). This was statistically significant when compared with the aggregate of the other AEDs ($P < 0.001$, OR = 6.87). Levetiracetam was also significantly ($P < 0.001$) associated with higher intolerability rate (17.7%), dose decreased rate (9.4%), and complete cessation rate (8.3%), when compared with the aggregate of the other AEDs. Zonisamide (ZNS) was also significantly associated with a higher rate of PBSE (9.7%) and IPBSE (7.9%, all $P < 0.001$). On the other hand, carbamazepine (CBZ), clobazam (CLB), gabapentin (GBP), lamotrigine (LTG), oxcarbazepine (OXC), phenytoin (PHT), and valproate (VPA) were significantly associated with a decreased PBSE rates ($P < 0.001$). Carbamazepine, GBP, LTG, PHT, and VPA were also associated with lower IPBSE rates when compared individually with the aggregate of other AEDs. All other AEDs were found to have intermediate rates that were not either increased or decreased compared with other AEDs. When each AED was compared to LTG, only CBZ had a significantly lower PBSE rate. The main limitations of this study were that the study design was retrospective and not blinded, and the AEDs were not randomly assigned to patients.
Conclusions: Psychiatric and behavioral side effects occur more frequently in patients taking LEV and ZNS than any other AED and led to higher rates of intolerability. Lower PBSE rates were seen in patients taking CBZ, CLB, GBP, LTG, OXC, PHT, and VPA. Our findings may help facilitate the AED selection process.

1. Introduction

Psychiatric and behavioral side effects (PBSEs) are highly prevalent in patients taking antiepileptic drugs (AEDs). These adverse effects can lead to suboptimal dosing for seizure control, as well as poor adherence to AEDs and early AED discontinuation in up 25% of patients [1,2]. Between 15% and 20% of adult patients with epilepsy taking AEDs experience PBSEs; these include depressive mood, psychosis, increase in irritability, and aggressive behavior [3]. Psychiatric and behavioral side effects are some of the most common adverse effects associated with AED use and have a higher cost per patient per year compared with other adverse-effect categories [4,5]. To our knowledge, no previous study has compared PBSEs of both newer and older AEDs while controlling for potential non-AED-related factors [6]. A better understanding of the PBSE profiles of different AEDs available today is

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important clinically, as it could help provide practical recommendations and guidelines for physicians to weigh the cost–benefit ratio when prescribing AEDs.

Of particular importance is that psychiatric and behavioral comorbidities result from the social and structural implications of epilepsy, as well as from the AEDs themselves [4]. Thus, individual susceptibility highlights the necessity of understanding patient-related, dose-independent factors that contribute to the onset of PBSEs [7,8]. Yet, our knowledge of the influence of these factors is still very limited [9]. In the current study, we compared PBSE profiles of older and newer AEDs using a large patient database. We also looked at the influence of patient demographics and medical histories, as well as AED dose and drug load, on the onset of PBSEs.

2. Methods

We examined the medical records of 4085 adult patients (≥18 years old) using the Columbia and Yale Antiepileptic Drug Database. We included patients seen at both the Columbia Comprehensive Epilepsy Center and the Yale Comprehensive Epilepsy Center, all of whom had been newly started on one or more of the following AEDs between January 1, 2000 and January 1, 2015, and were followed up for at least 1 year: carbamazepine (CBZ), clobazam (CLB), felbamate (FBM), gabapentin (GBP), lacosamide (LCM), levetiracetam (LEV), lamotrigine (LTG), oxcarbazepine (OXC), phenobarbital (PB), pregabalin (PGB), phenytoin (PHT), primidone (PRM), rufinamide (RFM), tiagabine (TGB), topiramate (TPM), vigabatrin (VGB), valproic acid (VPA), and zonisamide (ZNS). An AED was labeled as newly started in a patient if it was administered for the first time at our center.

We reviewed all patient medical records available at our center including office visit notes, written summaries of phone communications, and hospital and emergency discharge notes for documentation of AED regimens, side effects attributed to AEDs in patients, as well as 83 other variables including patient demographics, epilepsy characteristics, medical history (e.g., previous psychiatric condition, prior surgeries), treating physician, and other relevant factors (Supplementary Table 1). The epileptologists of the patients included in this study reviewed side effects from AEDs as a part of every patient clinic visit. Psychiatric side effects (PSEs) were categorized as depressive mood, psychosis, anxiety, and suicidal thoughts; and behavioral side effects (BSEs) were categorized as irritability, aggression, tantrum, and other behavioral problems (including hyperactivity and emotional lability/mood changes). The definitions of irritability, tantrum, and aggression were inconsistent in the literature, and there was much overlap between those definitions. In this study, irritability was a generally negative mood, often described as "grumpiness" or "crabbiness" by patients, associated with a decrease in magnitude of any trigger that was needed to elicit a negative emotional or angry response and/or a decrease in time to losing one's temper in response to a stimulus compared with patient's baseline. Tantrum was any severe outburst of anger or an angry reaction out of proportion to the stressor, often described by patients as "blowups" or "explosions". Aggression was any behavior aimed at causing harm to self or others. All PBSEs were recorded in our database, and attribution of PBSEs to a specific AED was based on our review of the epilepsy attending physician notes. A PBSE was only attributed to a particular AED if (1) the attending physician confirmed and attributed the PBSE to an AED; (2) the PBSE only occurred or aggravated after starting or increasing the dose of an AED (while the doses of other AEDs were held constant in polytherapy); and (3) for intolerable side effects, if the PBSE decreased in severity or was resolved after a dose reduction or discontinuation of an AED (while the doses of other AEDs were held constant in polytherapy). An intolerable PBSE (IPBSE) was defined as a PBSE that led to a decrease in dose or cessation of an AED.

In our study, we first looked for potential relationship between AED load and PBSE rate. This is done by first dividing the prescribed patient daily dose by the corresponding defined daily dose for an AED [10] assigned by the World Health Organization to obtain a dose ratio (Supplementary Table 2). Antiepileptic drug dose ratios were summed for each patient's AED regimen to obtain the AED load for each patient regimen [11]. We then calculated for each patient a mean AED load from regimens where the patient did not have PBSE and a mean AED load from regimens where the patient had PBSE. Finally, we compared the means of AED loads between patients who had PBSE and those that did not.

To account for factors that may influence the occurrence of PBSE, we tested 83 variables (listed in Supplementary Table 1) as potential non-AED predictors of PBSE. Subsequently, we calculated the rates of each PBSE and IPBSE for the entire cohort, and for each AED, in both monotherapy and polytherapy. Significant non-AED predictors were then controlled for in multivariate analysis when we compared the frequency of PBSEs attributed to a specific AED with the average PBSE rate of all other AEDs. Similar comparisons were done for IPBSEs, PSEs only, and BSEs only. Because previous studies have found evidence supporting that LTG is generally well tolerated with regard to PBSEs [3,12], we compared each AED's PBSE profile against that of LTG. Finally, we examined specific PBSEs individually and their frequencies associated with each AED.

The study was reviewed and approved by the Yale University Institutional Review Board.

2.1. Statistical analysis

This study used SAS version 9.3 to conduct all statistical analyses. To compare the means of dose ratios and AED loads between patients with PBSE and those without, a series of two-sample *t*-tests was performed. For each *t*-test, significance was set at $P < 0.05$. If the two-sample variances were similar ($P \geq 0.05$), the pooled variance estimator was used to calculate the P value. If the two-sample variances were significantly different ($P < 0.05$), the Satterthwaite's method was used to calculate the P value.

To determine which non-AED factors were associated with the overall rate of PBSEs, a series of univariate binary logistic regression analysis was performed followed by a multivariate binary logistic regression analysis. The dependent variable (whether a patient has experienced at least one PBSE) was dichotomous, and the independent variables were either dichotomous or continuous. Each independent variable was individually entered into a univariate logistic regression with the significance level set at $P < 0.05$. Variables that were significantly associated with overall rate of PBSE were then entered into a multivariable logistic regression. The Bonferroni method was applied; significance level was set at $P < 0.05$/number of variables.

To compare the rates of PBSEs between AEDs, the rate of each AED was compared with the average rates of the other AEDs using a logistic regression while controlling for significant non-AED covariates. Significance for this series of tests was set at $P < 0.05/18$ AEDs tested $= 0.003$ using the Bonferroni correction. A P value between 0.003 and 0.05 was considered a trend. The exact logistic regression was used if the analysis included expected values less than 5. The Bonferroni correction was also applied to other analyses based on number of tests carried out in each analysis.

3. Results

Our study population consisted of 4085 patients with epilepsy that started an AED at the age of 18 or older. Most of the patients were diagnosed with focal epilepsy (71.1%), followed by idiopathic generalized epilepsy (17.4%) and symptomatic generalized epilepsy (3.6%) (Table 1). A total of 79.8% (3261/4085) of our study population had seizures that failed to improve with two or more AEDs.

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Table 1
Demographics of adult (≥18 years old) patients with epilepsy on one of the AEDs.

AED	Number of patients	Men, %	Age, years, mean ± SD	Epilepsy type, %				Weight, kg, mean ± SD	Maximum dose, mg/day, mean ± SD
				Focal	Primary generalized	Symptomatic generalized	Unclear		
CBZ	1103	48.2	41 ± 14	82.5	7.8	4.2	5.5	77 ± 20	1011 ± 510
CLB	645	49.5	40 ± 15	83.4	6.2	6.5	3.9	77 ± 20	27 ± 14
FBM	184	41.9	38 ± 14	62.5	19.6	14.1	3.8	76 ± 21	2860 ± 1128
GBP	606	44.2	46 ± 16	83.2	6.3	4.5	6.1	74 ± 18	2027 ± 1561
LCM	354	44.4	40 ± 15	87.9	5.4	3.1	3.7	77 ± 21	342 ± 165
LEV	1890	45.1	42 ± 16	73.9	16.1	3.9	6.1	76 ± 20	2123 ± 1176
LTG	2337	43.0	41 ± 15	72.7	16.5	3.3	7.5	75 ± 19	488 ± 285
OXC	566	48.1	39 ± 16	87.3	3.2	3.4	6.2	76 ± 20	1486 ± 741
PB	234	39.3	43 ± 16	71.4	15.4	7.7	5.6	77 ± 23	120 ± 80
PGB	502	43.4	43 ± 16	86.9	2.0	5.8	5.4	75 ± 19	395 ± 316
PHT	816	54.0	45 ± 17	77.6	11.0	3.3	8.1	79 ± 21	379 ± 145
PRM	94	51.1	45 ± 17	71.3	18.1	8.5	2.1	74 ± 18	630 ± 374
RFM	131	40.5	37 ± 13	35.9	23.7	36.6	3.8	72 ± 21	2171 ± 1033
TGB	46	37.0	44 ± 16	87.0	2.2	4.4	6.5	73 ± 15	24 ± 16
TPM	639	33.8	38 ± 14	69.2	17.5	8.0	5.3	77 ± 23	289 ± 226
VGB	75	60.0	40 ± 14	81.3	1.3	17.3	0.0	73 ± 17	2907 ± 997
VPA	868	50.8	38 ± 15	45.4	39.3	8.8	6.6	77 ± 18	1502 ± 862
ZNS	760	38.0	38 ± 14	68.0	20.1	6.3	5.5	75 ± 22	367 ± 181
Overall	4085	44.9	41 ± 16	71.1	17.4	3.6	7.9	76 ± 20	

Abbreviations: AED: Antiepileptic Drug; CBZ: Carbamazepine; CLB: Clobazam; FBM: Felbamate; GBP: Gabapentin; LCM: Lacosamide; LEV: Levetiracetam; LTG: Lamotrigine; OXC: Oxcarbazepine; PB: Phenobarbital; PGB: Pregabalin; PHT: Phenytoin; PRM: Primidone; RFM: Rufinamide; TGB: Tiagabine; TPM: Topiramate; VGB: Vigabatrin; VPA: Valproate; ZNS: Zonisamide.

Overall, 17.2% (701/4085) of patients developed PBSE attributed to an AED, and 13.8% (565/4085) experienced intolerability. Irritability/moodiness was the most common PBSE (6.9%), followed by depressive mood (4.1%), anxiety (2.5%), other behavioral changes (1.6%), aggressive behavior (1.0%), psychosis (0.5%), tantrums (0.5%), and suicidal thoughts (0.2%). Among patients who had one AED-attributed PBSE, 17.8% (123/701) had another AED-attributed PBSE; among patients who had one AED-attributed IPBSE, 15.9% (90/565) had another AED-attributed IPBSE. The average rates of AED-attributed PBSE and IPBSE for a single AED were 7.2% and 5.6%, respectively, with 2.9% leading to dose reduction and 2.7% leading to AED cessation.

3.1. AED load

The average AED load of patients when they experienced PBSE (2.02 ± 1.51) was not significantly different from the average AED load of patients when they did not experience PBSE (2.07 ± 1.34) (Supplementary Table 3).

3.2. Factors associated with PBSEs

Out of the 83 variables that were individually tested for an association with PBSE incidence, 14 variables were significantly linked to PBSE in the univariate analysis ($P < 0.05$). When these 14 variables were entered into a backwards stepwise multivariable logistic regression model, 5 variables remained statistically significant or trended towards significance. History of any psychiatric condition(s), secondarily generalized seizures, absence seizures, and intractable epilepsy remained significantly associated with incidence of PBSE ($P < 0.05/5 = 0.01$), while history of static encephalopathy trended towards a significant association with incidence of PBSE ($0.01 < P < 0.05$) (Table 2).

3.3. Comparison of AED's overall PBSE profiles

Fig. 1 showed that significantly more PBSEs and IPBSEs were attributed to LEV and ZNS ($P < 0.003$) than average. Significantly less PBSEs were attributed to CBZ, CLB, GBP, LTG, OXC, PHT, and VPA ($P < 0.003$) than average. Tiagabine did not reach statistical significance but only trended towards being associated with a higher rate of PBSE than average, which might be due to the small number of patients and regimens. Lacosamide and PGB trended towards being associated with a lower rate of PBSE than average.

Significantly more IPBSEs were attributed to LEV and ZNS ($P < 0.003$). Tiagabine only trended towards being associated with a higher rate of IPBSE; however, it is important to note that all patients who experienced PBSE associated with TGB reduced drug dose or stopped the AED

Table 2
Non-AED factors associated with presence of PBSEs attributed to taking an AED in a multivariable model.

Predictor		% (*N*) with PBSE	Univariate P-value	Multivariate P-value	Multivariate odds ratio (95% CI)
History of psychiatric condition	Yes	22.3 (276)	<0.001	<0.001**	1.72 (1.44–2.07)
	No	13.1 (306)			
Seizures failed to improve with 2 or more AEDs	Yes	20.0 (652)	<0.001	<0.001**	3.17 (2.30–4.37)
	No	6.0 (49)			
History of secondarily generalized seizures	Yes	18.7 (408)	0.005	0.003**	1.35 (1.10–1.65)
	No	15.4 (293)			
History of absence seizures	Yes	22.1 (92)	0.005	0.007**	1.50 (1.12–2.02)
	No	16.6 (609)			
Static encephalopathy	Yes	24.0 (86)	<0.001	0.018*	1.46 (1.07–1.98)
	No	16.5 (615)			

* Statistical trend: $0.01 < P < 0.05$.
** Statistical significance: $P < 0.01$.

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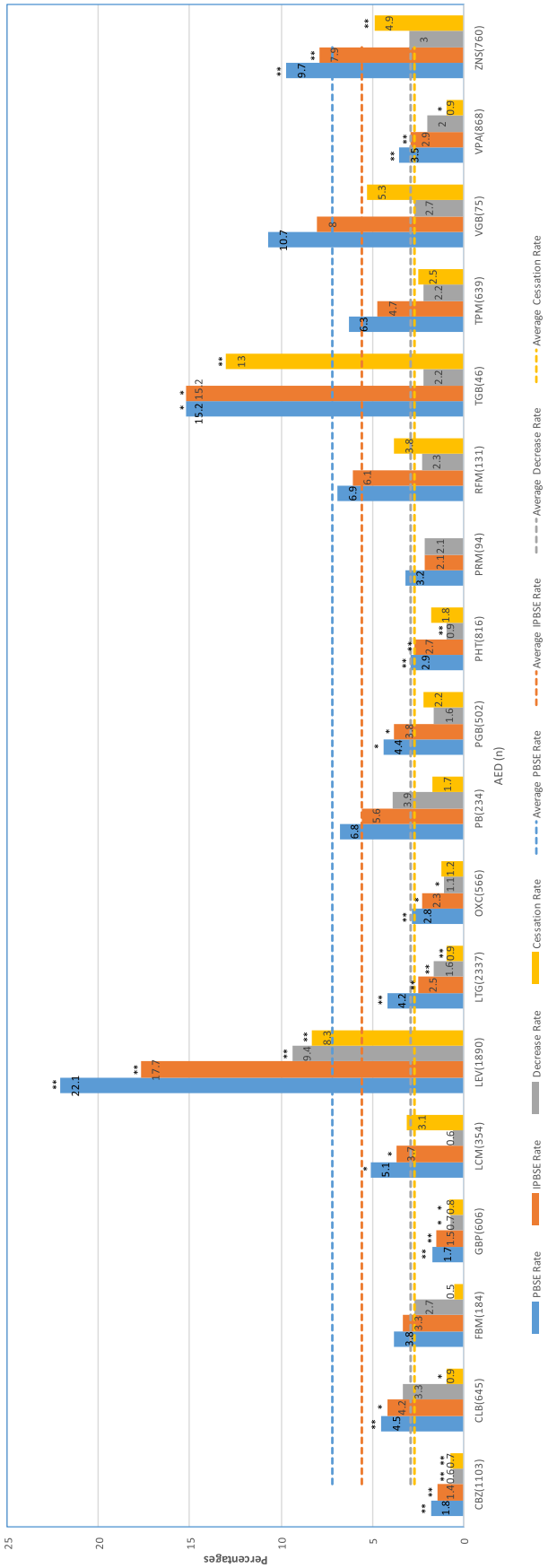

Fig. 1. Comparison of overall AED-attributed PBSEs in adults with epilepsy taking one of the AEDs. Abbreviations: AED, antiepileptic drug; CBZ, carbamazepine; CLB, clobazam; FBM, felbamate; GBP, gabapentin; IPBSE, intolerable psychiatric and behavioral side effect; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PBSE, psychiatric and behavioral side effect; PGB, pregabalin; PHT, phenytoin; PRM, primidone; RFM, rufinamide; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; VPA, valproate; ZNS, zonisamide. Analysis adjusted for history of psychiatric conditions, history of absence seizures, and seizures failing to improve with two or more AEDs. * Statistical trend: 0.003 < P < 0.05. ** Statistical significance: P < 0.003.

Table 3
Comparison of specific AED-attributed PBSEs in adults with epilepsy taking one of the AEDs‡.

		Behavioral side effects % (n)				Psychiatric side effects % (n)			
AED	n	Irritability (280)	Aggression (n=39)	Tantrum (n=21)	Other behavioral problems (n=64)	Depressive mood (n=168)	Psychosis (n=19)	Anxiety (n=103)	Suicidal thoughts (n=7)
CBZ	1103	**0.5 (6)[a]**	0.2 (2)	0.1 (1)	**0.2 (2)[a]**	**0.9 (10)[a]**	–	**0.2 (2)[a]**	–
CLB	645	**1.7 (11)[a]**	0.8 (5)	0.3 (2)	0.8 (5)	1.4 (9)	0.2 (1)	0.5 (3)	0.2 (1)
FBM	184	2.7 (5)	–	–	1.1 (2)	0.5 (1)	0.5 (1)	–	–
GBP	606	**1.0 (6)[a]**	–	–	0.2 (1)	**0.7 (4)[a]**	0.2 (1)	–	–
LCM	354	**1.4 (5)[a]**	0.6 (2)	0.6 (2)	0.6 (2)	1.1 (4)	0.3 (1)	1.4 (5)	0.3 (1)
LEV	1890	**12.5 (236)[b]**	**1.4 (27)[b]**	**0.7 (14)[b]**	**2.5 (47)[b]**	**7.3 (138)[b]**	**0.6 (11)[b]**	**2.5 (47)[b]**	0.2 (4)
LTG	2337	**1.2 (27)[a]**	**0.1 (3)[a]**	0.1 (3)	**0.5 (11)[a]**	**1.2 (28)[a]**	0.1 (3)	**1.5 (34)[b]**	–
OXC	566	**0.5 (3)[a]**	0.2 (1)	–	0.4 (2)	1.8 (10)	–	0.5 (3)	–
PB	234	0.4 (1)	0.9 (2)	0.4 (1)	0.4 (1)	4.7 (11)	–	1.3 (3)	–
PGB	502	**1.6 (8)[a]**	0.2 (1)	**0.6 (3)[b]**	0.6 (3)	1.8 (9)	–	0.8 (4)	–
PHT	816	**0.5 (4)[a]**	0.1 (1)	–	0.4 (3)	1.6 (13)	–	0.7 (6)	0.1 (1)
PRM	94	1.1 (1)	–	–	–	2.1 (2)	–	–	–
RFM	131	1.5 (2)	1.5 (2)	–	**3.1 (4)[b]**	–	0.8 (1)	–	–
TGB	46	**10.9 (5)[b]**	–	–	–	4.4 (2)	**2.2 (1)[b]**	**4.4 (2)[b]**	–
TPM	639	2.8 (18)	0.5 (3)	0.2 (1)	1.1 (7)	2.2 (14)	0.2 (1)	0.8 (5)	–
VGB	75	2.7 (2)	–	**1.3 (1)[b]**	4.0 (3)	–	**2.7 (2)[b]**	5.3 (4)	–
VPA	868	**1.3 (11)[a]**	0.1 (1)	–	0.7 (6)	1.5 (13)	–	0.5 (4)	0.1 (1)
ZNS	760	3.2 (24)	0.4 (3)	0.1 (1)	1.1 (8)	**4.3 (33)[b]**	**0.8 (6)[b]**	1.3 (10)	–
Average		3.2	0.5	0.2	0.9	2.5	0.2	1.1	0.1
Statistical significance: P < 0.003		**Statistical trend: 0.003 < P < 0.005**							

‡Corrected for history of psychiatric condition, secondarily generalized epilepsy, absence seizures, and epilepsy intractability.
[a]Lower rate than the average of other AEDs.
[b]Higher rate than the average of other AEDs.
Abbreviations: AED, antiepileptic drug; CBZ, carbamazepine; CLB, clobazam; FBM, felbamate; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PGB, pregabalin; PHT, phenytoin; PRM, primidone; RFM, rufinamide; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; VPA, valproate; ZNS, zonisamide.

completely. Significantly less IPBSEs were attributed to CBZ, GBP, LTG, PHT, and VPA ($P < 0.003$).

Supplementary Fig. 1 showed that when analyzing monotherapy data alone, the overall trend of PBSE rates were similar for all AEDs compared with the corresponding rates seen in the overall analysis. In the monotherapy analysis, PBSE and IPBSE rates of LEV remained significantly higher compared with the average, and the PBSE and IPBSE rates of CBZ were significantly lower than the average. Valproate trended towards a lower PBSE rate, while both lamotrigine and valproate both trended towards lower IPBSE rates.

Table 4
Comparison of specific AED-attributed IPBSEs in adults with epilepsy taking one of the AEDs‡.

		Intolerable behavioral side effects % (n)				Intolerable psychiatric side effects % (n)			
AED	n	Irritability (223)	Aggression (n=33)	Tantrum (n=16)	Other behavioral problems (n=53)	Depressive mood (n=138)	Psychosis (n=16)	Anxiety (n=79)	Suicidal thoughts (n=7)
CBZ	1103	**0.5 (6)[a]**	0.2 (2)	0.1 (1)	**0.2 (2)[a]**	**0.5 (6)[a]**	–	**0.1 (1)[a]**	–
CLB	645	1.4 (9)	0.8 (5)	0.3 (2)	0.6 (4)	1.4 (9)	0.2 (1)	0.5 (3)	0.2 (1)
FBM	184	2.2 (4)	–	–	1.1 (2)	0.5 (1)	0.5 (1)	–	–
GBP	606	**1.0 (6)[a]**	–	–	–	**0.7 (4)[a]**	0.2 (1)	–	–
LCM	354	1.1 (4)	0.6 (2)	0.6 (2)	0.3 (1)	0.9 (3)	0.3 (1)	0.6 (2)	0.3 (1)
LEV	1890	**9.8 (185)[b]**	**1.2 (22)[b]**	**0.5 (9)[b]**	**2.3 (44)[b]**	**6.1 (116)[b]**	**0.5 (9)[b]**	**1.9 (35)[b]**	0.2 (4)
LTG	2337	**0.8 (19)[a]**	0.0 (1)	0.0 (1)	**0.3 (6)[a]**	**0.6 (15)[a]**	0.1 (2)	0.9 (21)	–
OXC	566	**0.5 (3)[a]**	0.2 (1)	–	0.4 (2)	1.2 (7)	–	0.4 (2)	–
PB	234	0.4 (1)	0.9 (2)	0.4 (1)	0.4 (1)	3.9 (9)	–	0.9 (2)	–
PGB	502	1.4 (7)	0.2 (1)	**0.6 (3)[b]**	0.4 (2)	1.2 (6)	–	0.8 (4)	–
PHT	816	**0.4 (3)[a]**	0.1 (1)	–	0.4 (3)	1.6 (13)	–	0.6 (5)	0.1 (1)
PRM	94	1.1 (1)	–	–	–	1.1 (1)	–	–	–
RFM	131	1.5 (2)	1.5 (2)	–	**3.1 (4)[b]**	–	–	–	–
TGB	46	**10.9 (5)[b]**	–	–	–	2.2 (1)	**2.2 (1)[b]**	**4.4 (2)[b]**	–
TPM	639	1.7 (11)	0.3 (2)	0.2 (1)	1.1 (7)	1.9 (12)	0.2 (1)	0.6 (4)	–
VGB	75	1.3 (1)	–	–	2.7 (2)	–	**2.7 (2)[b]**	5.3 (4)	–
VPA	868	**1.3 (11)[a]**	0.1 (1)	–	0.6 (5)	1.2 (10)	–	0.2 (2)	0.1 (1)
ZNS	760	2.8 (21)	0.4 (3)	0.1 (1)	0.8 (6)	**3.3 (25)[b]**	**0.8 (6)[b]**	1.2 (9)	–
Average		2.5	0.4	0.2	0.8	2.0	0.2	0.8	0.1
Statistical significance: P < 0.003		**Statistical trend: 0.003 < P < 0.005**							

‡Corrected for history of psychiatric condition, secondarily generalized epilepsy, absence seizures, and epilepsy intractability.
[a]Lower rate than the average of other AEDs.
[b]Higher rate than the average of other AEDs.
Abbreviations: AED, antiepileptic drug; CBZ, carbamazepine; CLB, clobazam; FBM, felbamate; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PGB, pregabalin; PHT, phenytoin; PRM, primidone; RFM, rufinamide; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; VPA, valproate; ZNS, zonisamide.

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3.4. Comparison of PSE profiles of AEDs

When only examining PSEs, 8.6% (353/4085) experienced PSE. We found that history of any psychiatric condition, intractable epilepsy, and static encephalopathy were non-AED factors associated with PSE risk (Supplementary Table 4). Supplementary Fig. 2 showed that after controlling for these factors, significantly more PSEs and IPSEs were attributed to LEV and ZNS. Significantly less PSEs were associated with CBZ and GBP, and less IPSEs were associated with CBZ and LTG compared with the average. Lamotrigine, PGB, PHT, and VPA trended towards lower PSE rates compared with the average.

3.5. Comparison of BSE profiles of AEDs

Examining only BSEs showed that 10.6% (431/4085) experienced BSE. History of intractable epilepsy, static encephalopathy, secondarily generalized seizure, and absence seizure were non-AED factors associated with BSE risk (Supplementary Table 5). Supplementary Fig. 3 showed that, after controlling for these factors, significantly more BSEs and IBSEs were attributed to LEV. More IBSEs were also attributed to TGB compared with the average. Significantly less BSEs and IBSEs were attributed to CBZ, GBP, LTG, OXC, PHT, and VPA. Phenobarbital trended towards lower BSE rate compared with the average.

3.6. Comparison of PBSE rates between LTG and other AEDs

Supplementary Figs. 4a and b showed that LEV, TGB, and ZNS had significantly higher PBSE and IPBSE rates compared with LTG. Carbamazepine's rate of PBSE was significantly lower compared with LTG, whereas GBP's PBSE rate and RFM's IPBSE rate were lower than those of LTG, respectively, but remained only trends (Supplementary Fig. 4a and b). When examining PSEs only, LEV and ZNS had higher rates of PSE compared with LTG (Supplementary Fig. 4c). When examining BSEs only, LEV, TGB, TPM, and ZNS all had higher rates of BSEs compared with LTG (Supplementary Fig. 4d).

3.7. Individual PBSE analysis

Table 3 showed that LEV was associated with higher rates of irritability, depressive mood, anxiety, aggression, and other behavioral problems. Zonisamide was associated with a higher rate of depressive mood. Lamotrigine, CBZ, and PHT were all associated with lower rates of irritability compared with the average. Lamotrigine was also associated with a significantly lower rate of depressive mood.

Table 4 showed that the results of intolerabilities caused by the individual PBSEs were similar. Levetiracetam was linked to higher rate of intolerability due to irritability, aggression, depressive mood, anxiety, and other behavioral problems. Tiagabine was associated with a higher rate of intolerability due to irritability. Pregabalin was associated with a higher rate of intolerability by tantrum. Carbamazepine and PHT were linked to lower rates of intolerability by irritability. Lamotrigine was associated with lower rates of intolerability by irritability and depressive mood.

4. Discussion

Previous literature has shown that the presence of psychiatric history is a strong predictor of PBSE with AED use in adult patients with epilepsy [3,4,13–15]. This finding was confirmed by our study. In addition, our study also found that patients with intractable epilepsy (seizures failing to improve with two or more AEDs), secondarily generalized seizures, or absence seizures are more likely to have PBSE when taking AEDs. History of static encephalopathy was also moderately associated with risk of PBSE. Intractable epilepsy has been linked to significant psychiatric problems that can decrease the patient's quality of life and increase the suicidal risk [16–19]. Although no previous study has shown that patients with secondarily generalized seizures had a higher risk of experiencing PBSEs, there is evidence suggesting that secondarily generalized seizure is associated with negative preictal (as auras) and postictal behavioral and psychiatric symptoms such as depressed mood, psychosis, anger, irritability, aggression, and nervousness [20–25]. Patients who have secondarily generalized seizures therefore are more likely to experience these behavioral and psychiatric symptoms. However, whether susceptibility to these symptoms in these patients is directly related to higher PBSE rates when taking AEDs needs to be further investigated. To our knowledge, there have not been any studies that examined or showed an association between history of absence seizure and PBSE incidence by AED. Our study was the first study to show that patients who had been diagnosed with absence seizures were more likely to have PBSEs.

Our results suggest that history of absence seizure and secondarily generalized seizure may influence physiological mechanisms that may also increase one's susceptibility to PBSEs of AED, although the specific mechanism(s) shared is not known at this point and may warrant further investigation in future studies. A recent study by Caplan et al. found that absence epilepsy was associated with attention-deficit hyperactivity disorder and affective/anxiety disorders [26], which suggested a possibility that the involvement of the thalamus in patients with absence epilepsy may predispose patients to develop PBSEs via mechanism(s) yet unknown.

A previous study published by Canevini et al. showed that there was no overall correlation between AED load and any side effects [11]. Our study specifically looked at the link between AED-attributed PBSE and AED load, and we also concluded that there was no evidence showing a correlation between AED load and PBSE rate.

To our knowledge, our study was the first study to compare PBSE rates of different newer and older AEDs in a large population of patients with epilepsy while controlling for non-AED factors linked to PBSE incidence. When we controlled for non-AED factors that were linked to PBSE, we found that patients taking LEV and ZNS experienced significantly more PBSEs and IPBSE than average. Psychiatric and behavioral side effects related to LEV and ZNS have been documented in literature. Previous studies have shown that the primary reasons for discontinuing LEV in patients with epilepsy were due to PBSEs, and approximately 10% to 24% of patients with epilepsy taking LEV developed PBSEs [3,14,15,27]. Previous literature has shown that patients with preexisting psychiatric disorders might be at a higher risk of developing PBSEs attributed to LEV, possibly related to genetic predisposition [27,28]. In agreement with our findings, irritability has been found to be the most common PBSE reported with LEV use [29]. Incidence of irritability has been shown to be similar across different LEV doses [29]. Other PBSEs such as depression, anxiety, and emotional liability have been reported to occur in around 3% of patients with epilepsy who used LEV, whereas psychosis and suicidal events had been reported lower at around 1% [30]. Psychiatric and behavioral side effects have been found to be the most common reasons for discontinuing ZNS [3,31], and depressive mood was the most common PBSE linked to ZNS, followed by irritability. A recent study showed that depression was the most common PBSE with ZNS use (2.5%), followed by aggressive behavior (1.8%), psychosis (1.4%), and irritability (1.2%) [31]. However, since the population demographics and methodologies used between that study and ours were different, it would be difficult to compare the results. Additional controlled trials and meta-analysis should be done to further clarify the potential association between ZNS use and PBSEs.

On the other hand, we found in our study that lower rates of PBSEs were associated with CBZ, CLB, GBP, LTG, OXC, PHT, and VPA. The link between CBZ use and PBSE incidence had been extensively studied in the literature, and it had been shown that PBSEs were infrequently associated with CBZ [32]. Most of the studies that examined the PBSE profile of CLB were done in pediatric populations. One randomized

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trial and several retrospective studies in children showed that CLB was linked to higher PBSE rates compared with CBZ and PHT, with reportedly higher incidence rates and discontinuation rates than those found in our study [32]. Gabapentin had been shown to be linked to fewer PBSEs compared with VGB and LTG in adults with learning disabilities [33]. The most common PBSEs associated with GBP were reported to be anxiety/agitation and depression in the SANAD study [34]. The SANAD study also found PBSEs to be infrequent with OXC use [34]. One retrospective study found some evidence that OXC was linked to aggression in a small number of children [32], whereas another study found no relationship between OXC and PBSE in children with benign childhood epilepsy [35]. Phenytoin had been shown to be associated with a very low PBSE rate by large randomized studies, significantly lower than CLB, PB, and PRM [32]. Large studies had indicated a low PBSE rate with VPA use similar to the rate found in our study, with behavior change/aggression and depression being the two most common PBSEs associated with VPA. A low rate of PBSE associated with LTG had been well documented in the literature [3,12,36]. In addition, LTG had been found in a study to be protective against PBSEs associated with LEV when both AEDs were given together [14]. In our study, the only AED with lower PBSE rate compared with LTG was CBZ. Mixed results have been shown in previous studies. A trial by Meador et al. found that LTG was associated with significantly less behavioral side effects compared with CBZ [37]; however, the study had 25 subjects all of which were healthy participants, compared with our study sample of patients with diagnosed epilepsy. Another trial in older patients with epilepsy showed that there were no differences in certain PBSEs such as temper and anxiety when comparing LTG and CBZ [38].

There were several limitations in our study. Some of the main limitations include the following: (1) the data collected were retrospective in nature; (2) the study was not blinded, and patients were not randomly assigned AEDs; and (3) patients were not given questionnaires or interviews specifically evaluating PBSEs after using AEDs. However, we minimized potential bias and error by identifying non-AED predictors of PBSEs, controlling for these predictors in our analysis using a multivariable logistic regression model, and using a more conservative alpha level based on the Bonferroni method. Another limitation of our study was the exclusion of newer AEDs such as eslicarbazepine, ezogabine, and perampanel. In the current study, we did not include these newer AEDs in our analysis because of very small sample sizes of patients who took these AEDs for at least 1 year in our data set. Perampanel, a selective noncompetitive antagonist AMPA-type glutamate receptor antagonist, appears to be related to a high rate of PBSE similar to that of LEV, particularly irritability and aggression [39–42]. Levetiracetam binds selectively to the synaptic vesicle protein 2A (SV2A) to modulate synaptic transmission [43], but there is also evidence that LEV also have modulatory activity on AMPA receptors [44]. Based on evidence that perampanel and LEV both act on the AMPA receptor, future studies may focus on investigating whether the effect on AMPA receptors is associated with the high rates of PBSEs observed in both AEDs. Further evidence supporting this hypothesis comes from a recent study that showed that brivaracetam (BRV), a more potent selective ligand of SV2A than LEV that has no modulatory activity on the AMPA receptor [43], is associated with significantly less PBSEs compared with LEV [45]. Finally, because of the inconsistency in the definitions of irritability, tantrum, and aggression in the literature, as well as the potential varied subjective interpretation by patients, the incidence rates on individual PBSEs presented in our study need to be scrutinized and further examined by future studies in order to provide better understanding of these related phenomena and their association with AED use.

Psychiatric and behavioral side effects are common among patients with epilepsy that use AEDs, particularly in patients with a history of psychiatric conditions, intractable seizures, secondarily generalized seizures, and absence seizure. Adult patients using LEV and ZNS for treatment of epilepsy may also be at a higher risk of developing PBSEs compared with those using other available AEDs and are also more likely to stop or reduce dose of AED because of PBSEs. The findings in our study may serve as preliminary guidelines for clinicians when prescribing AEDs for patients with epilepsy and considering side effect profiles of AEDs. Patients who are mainly concerned about PBSEs associated with AED may consider replacing LEV and/or ZNS with AEDs associated with lower incidences of PBSEs such as LTG, CBZ, or GBP.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2017.08.039.

Conflict of interest statement

None of the authors has any conflict of interest to disclose.

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