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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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