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Cross-sensitivity of psychiatric and behavioral side effects with antiepileptic drug use

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ABSTRACT

Purpose: To determine rates of cross-sensitivity of intolerable psychiatric and behavioral side effects (IPBSEs) among commonly used antiepileptic drugs (AEDs) in adult patients with epilepsy.
Methods: IPBSE was defined as a psychiatric or behavioral side effect attributed to AED use that led to a decrease in dose or cessation of an AED. Cross-sensitivity was calculated and was defined as the likelihood of developing IPBSE to a specific AED given IPBSE to another AED. Our sample consisted of 2312 adult patients that were prescribed 2 or more AEDs. Non-AED confounders and were controlled for in all analyses.
Results: Among the 2312 patients, 20.2% of patients who had taken at least 2 AEDs had IPBSE(s) attributed to at least one AED; 3.5% had IPBSE to two or more AEDs. History of treated depression and psychosis were found to be significant predictors ($p < 0.001$) of developing IPBSE and were controlled for in all AED-specific analyses. Cross-sensitivity was seen between LEV and ZNS ($p < 0.001$). There was a significant increase in odds of experiencing IPBSE to LEV (41.5%; OR = 2.7; $p < 0.001$) or ZNS (22.1%; OR = 3.5; $p < 0.001$) given a patient had IPBSE to another AED compared to having no IPBSE to other AEDs (20.5% and 7.5%, respectively).
Conclusion: History of depression and psychosis increased risk of developing IPBSE to AEDs. The probability of experiencing IPBSE increased for a patient taking LEV or ZNS if the patient experienced IPBSE to another AED. Our results may be clinically useful for predicting IPBSE associated with certain AEDs.

1. Introduction

It is well established in the literature that psychiatric and behavioral side effects (PBSE) are common in patients using antiepileptic drugs (AED) [1–4]. These adverse effects can range from minor behavioral changes to debilitating depressive symptoms and even suicidality [1–6]. PBSEs may oftentimes lead to discontinuation of medication, and it has been reported by several studies that previous psychiatric history is a highly important independent predictor of PBSE incidence in epilepsy patients using AEDs [1–4]. Since AEDs are the mainstay of epilepsy treatment, the benefits of seizure control must be carefully weighed against potential AED adverse effects. It has been reported that PBSEs negatively influence patients' quality of life and can be more detrimental than the seizures they are designed to treat [7]. Moreover, approximately 40–50% of epilepsy patients take more than one AED in their lifetime [8–11], and the occurrence of PBSE may increase as the number of AEDs a patient takes increases [12]. It may be clinically relevant and useful therefore to gather information on the likelihood of a patient developing PBSE to an AED given the patient has an PBSE to another AED, or what we defined as PBSE cross-sensitivity in this study. Such information may aid the AED selection process and can potentially minimize the occurrence of psychiatric or behavioral adverse effects caused by AEDs.

PBSEs are difficult to predict in patients taking AEDs, but there are some evidence that age, sex, psychiatric history, and genetic variations may be risk factors for developing psychiatric side effects [3,13,14]. Cross-sensitivity among specific AEDs has been reported with adverse effects such as skin rash and with adverse cognitive effects [15–21]. However, potential cross-sensitivities of PBSEs amongst AEDs are not known in the literature and can be difficult to predict. Knowledge of such cross-sensitivities among AEDs is very important in clinical practice, particularly for patients at high risk for developing PBSE's such as patients with psychiatric comorbidities.14] The objective of our present study is to examine potential PBSE cross-sensitivities between the most

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common AEDs used at our center by retrospectively reviewing the incidence of PBSE, using the same criteria and definitions for all patients while controlling for potential confounding variables.

2. Methods

We conducted a retrospective review using the Columbia and Yale Antiepileptic Drug Databse, which included patient background, medical history, AED use, side effects, AED intolerability, epilepsy characteristics, and other relevant variables for 2312 adult patients (≥18 years of age) that were taking at least 2 AEDs, and were followed up for at least 1 year at the Columbia Comprehensive Epilepsy Center or the Yale Comprehensive Epilepsy Center. Epilepsy and seizure types were defined using the newest ILAE classification [22,23]. In our review, we included office visit notes, written summaries of phone communications, and hospital and emergency discharge notes for documentation of AED regimens. Side effects from AEDs were reviewed and confirmed by each patient's epileptologist as part of every patient clinic visit. Psychiatric side effects included depressive mood, psychosis, anxiety, and suicidal thoughts; and behavioral side effects included irritability, aggression, tantrum, and other behavioral problems (including hyperactivity and emotional lability/mood changes), as reported by the patient to the treating epileptologist. Due to inconsistency of the definitions of irritability, tantrum, and aggression in the current literature, we decided to use the following definitions in this study. Irritability was a negative mood often described as "grumpiness" or "crabbiness" by patients, associated with a lower threshold required to elicit a negative emotional response or anger compared with patient's baseline. Tantrum was any severe outburst of anger or an angry reaction out of proportion to the stimulus, often described by patients as "blowups" or "explosions". Aggression was any behavior aimed at causing harm to self or others.

A PBSE was only attributed to an AED if 1) the patient reported the symptom and the treating attending epileptologist attributed the PBSE to an AED, and 2) the PBSE only occurred or worsened, as reported by the patient, after starting or increasing the dose of an AED (while the doses of other AEDs were held constant in polytherapy). In this study, an intolerable PBSE (IPBSE) was defined as a PBSE that resulted in a decrease in dose or cessation of an AED thought to causing PBSE; cross-sensitivity was defined as the likelihood of developing IPBSE to a specific AED given one or more IPBSEs to another AED. The AEDs included in this study were carbamazepine (CBZ), felbamate (FBM), gabapentin (GBP), lacosamide (LCM), levetiracetam (LEV), lamotrigine (LTG), oxcarbazepine (OXC), phenobarbital (PB), pregabalin (PGB), phenytoin (PHT), primidone (PRM), tiagabine (TGB), topiramate (TPM), vigabatrin (VGB), valproic acid (VPA), and zonisamide (ZNS).

2.1. Non-AED predictor

To investigate non-AED predictors of experiencing IPBSE to 2 or more AEDs, we examined 83 non-AED variables (Supplementary Table 1), which included various demographics, medical, and epilepsy-related variables such as seizure type. To evaluate the possible predictors of IPBSE, we first performed univariate analysis using a simple logistic regression model to predict the occurrence of IPBSE. 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 the dependent variable using a $p < 0.05$ cutoff were then entered into a multivariable logistic regression. The multivariable logistic regression analysis allowed us to test for associations between each variable controlling for other variables in the model and to investigate the extent to which these variables explained the observed between-patient variation in IPBSE. Significance for multivariable logistic regression analysis was set using the Bonferroni correction at $p = 0.05$/number of variable in multivariable logistic regression. Data was analyzed using SAS v.9.3. We considered a trend to be present if the p-value was between the Bonferroni cutoff and 0.05.

2.2. Rates of specific IPBSE cross-sensitivity

For each AED, we calculated the rate of having IPBSE to drug X in those who had IPBSEs to drug Y, and compared that to the rate of having IPBSE to drug X in those who took drug Y but did not have IPBSEs. If the former was significantly higher than the latter, we considered this to indicate cross-sensitivity. To determine significance, we used either a multivariable logistic regression or an exact logistic regression model (if expected sample size < 5), and adjusted for significant non-AED predictors of experiencing IPBSE to 2 or more AEDs. A p-value < 0.001 was considered statistically significant, while a p-value between 0.05 and 0.001 was considered a trend.

3. Results

Our sample consisted of 2312 patients who had taken ≥2 AEDs; 20.2% (468/2312) had IPBSE(s) attributed to at least one AED, and 3.5% (81/2312) developed IPBSE to 2 or more AEDs. Most of our patients had focal epilepsy (71%). Lamotrigine and LEV were the two most commonly prescribed AEDs. A description of the demographics of the sample is displayed in Table 1.

3.1. Non-AED predictors analysis

Out of the non-AED variables tested, history of treated depression (OR = 3.2, 95% CI: 2.0–4.9) and history of psychosis (OR = 4.4, 95% CI: 2.0–9.5) were significantly associated with IPBSE to 2 or more AEDs in our multivariable logistic regression analysis (Table 2).

3.2. Rates of IPBSE cross-sensitivity

Table 3 shows an abridged version containing cross-sensitivity analyses with AEDs that had at least 15 patients with IPBSEs. Cross-sensitivity results below are reported and abbreviated using the following nomenclature in patients who had an IPBSE to LEV and took LTG, 4.9% had IPBSE to LTG (abbreviated as LEV→LTG: 4.9%). It should be noted that the reporting of cross-sensitivity rates between an AED pair (for example, LEV → LTG and LTG → LEV), does not imply that one drug was administered before the other, but it simply shows that there was IPBSE to the first drug and the second drug was also administered, either before or after the administration of the first drug.

Significant cross-sensitivity was seen between LEV and ZNS ($p < 0.001$). Of patients who had IPBSE to LEV and took ZNS, 24.1% had IPBSE to ZNS (LEV → ZNS: 24.1%); compared to patients who took LEV and did not have IPBSE, the rate of IPBSE with ZNS was 8.4. Of patient who had IPBSE to ZNS and took LEV, 47.6% had IPBSE to LEV (ZNS → LEV: 47.6%); compared to patients who took ZNS and did not have IPBSE, the rate of IPBSE with LEV was 20.8%.

Although not statistically significant, a trend was seen for cross-sensitivity between LEV and LTG ($0.001 < p < 0.05$).

Of patients who had IPBSE to any AED other than LEV and took LEV, 41.5% had IPBSE to LEV; however, if a patient had no IPBSEs to any other AED, the rate of PBSE with LEV was 20.5% (OR = 2.7; $p < 0.001$). Of patients who had IPBSE to any AED other than ZNS and took ZNS, 22.1% had PBSE to ZNS; however, if a patient had no IPBSEs to any other AED, the rate with ZNS was 7.5% (OR = 3.5; $p < 0.001$). The odds of experiencing IPBSE to VPA given a patient had IPBSE to another AED trended toward significance (7.3% vs 2.2%; OR = 3.0; $0.001 < p < 0.05$).

4. Discussion

Our study showed that having IPBSE to specific AEDs increased the