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Rates and predictors of patient-reported cognitive side effects of antiepileptic drugs: An extended follow-up

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ABSTRACT

Purpose: Impact of adverse effects of antiepileptic medications (AEDs) such as cognitive side effects (CSEs) on quality of life can be significant. Here we provide an extended follow-up to our earlier study to investigate the predictors of cognitive side effects (CSEs) and relative frequency of CSEs among all commonly used AEDs.
Methods: In this retrospective study, medical records of 2860 adult outpatients with epilepsy seen at our center over a 12-year period who had taken one or more AEDs were examined.
Results: Of 2860 patients, 15% had intolerable CSEs attributed to at least one AED. On multiple logistic regression analysis, independent predictors of intolerable CSEs were lack of intellectual disability and polytherapy. In polytherapy, we found that intolerable CSEs were most commonly seen with topiramate (22.8% of 281 patients), significantly more than with almost all other AEDs. This was true in monotherapy as well, with significantly more intolerable CSEs occurring with topiramate (18.5% of 54 patients) than with gabapentin, carbamazepine, lamotrigine, and levetiracetam. AEDs with consistently low rates of ICSEs included gabapentin, pregabalin, lamotrigine, levetiracetam and carbamazepine.
Conclusion: These data can help facilitate selection of AEDs.

1. Introduction

Antiepileptic medications (AEDs) remain the mainstay of treatment in epilepsy. Currently, over 20 FDA-approved AEDs are available for use in management of patients with epilepsy. Adverse effects resulting from AEDs are common. The impact of adverse effects on the overall health, as assessed with quality of life (QOL) scales, is significant, with adverse medication effects having the strongest correlation with health-related QOL in one study [1]. Among a number of potential adverse effects that can result from the use of AEDs, subjective cognitive side effects (CSEs) may necessitate either discontinuation or dose reduction if symptoms are felt to be intolerable.

In a previous study by our group [2], we examined the prevalence of CSEs among commonly used AEDs and the potential predictors of CSEs among 1694 adult epilepsy patients followed at a single tertiary care center between 2000 and 2005. Since our previous paper, several new AEDs have been approved by the FDA. The newly approved AEDs include lacosamide, pregabalin, rufinamide, vigabatrin and clobazam (although the latter two were included in the prior study via importation from other countries). Also, some medications have become much more popular, such as levetiracetam [3]. Although some studies indicate that the risk of CSEs of the newly approved AEDs may be favorable [4,5], few data exist on comparison of CSEs of these new AEDs against all available AEDs.

We herein report an extended follow-up of our prior study, adding 1166 patients and 3 new AEDs with follow-up data up to year 2012 (7 years later than the prior study). We examined the relative frequency of CSEs attributed to specific AEDs, including the 5 recently approved AEDs. We also investigated the non-AED predictors of CSEs. With longer follow-up, more patients, and inclusion of 5 new AEDs, this study provides a more comprehensive

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picture of current clinical experience regarding AED-related subjective CSEs.

2. Materials and methods

Methodology was similar to that of our prior publication [2]. We reviewed the medical charts of 2860 adult (at least 16 years of age at first visit) outpatients seen by their treating epilepsy attending at the Columbia Comprehensive Epilepsy Center between January 1, 2000 and November 19, 2012 and with outcome available for at least one AED trial. During the 12-year study period, of the 2860 patients, 2192 patients were started on one or more AEDs at our center. AEDs started for the first time at our center were classified as "newly started" AEDs (carbamazepine [CBZ], clobazam [CLB], felbamate [FBM], gabapentin [GBP], lacosamide [LCM], levetiracetam [LEV], lamotrigine [LTG], oxcarbazepine [OXC], Phenobarbital [PB], phenytoin [PHT], pregabalin [PGB], primidone [PRM], rufinamide [RFM], tiagabine [TGB], topiramate [TPM], vigabatrin [VGB], valproic acid [VPA], or zonisamide [ZNS]).

Documentation of CSEs that developed during the use of any AED was obtained by review of all available notes in the medical chart, including review of a symptom checklist completed at each visit, telephone notes, and physician notes. Attribution of subjective CSEs to a particular AED was made based on physician notes. Cognitive side effects were categorized as one of the following: (1) language problems such as aphasia, anomia/word-finding difficulty, (2) memory difficulty, or (3) psychomotor/cognitive slowing, confusion/disorientation or encephalopathy. "Intolerable" CSEs (ICSEs) were defined as CSEs attributed to an AED resulting in dose reduction or discontinuation of that AED. In the situation of multiple concomitant AEDs, CSE attribution to an AED was made only if the medical chart specified an AED.

Data abstraction based on review of medical records included patient characteristics including medical and psychiatric history, concomitant medications and dosages, laboratory test results, side effects, and efficacy measures. Data were entered into an electronic database by trained research assistants. As there was one person entering data per patient medical record, no inter-rater reliability was evaluated. However, on a regular basis, the physician investigator performed random review of data entered by all research assistants. Additionally, automatic error reports were generated, for example, highlighting inconsistencies between syndrome and seizure type. Other possible errors were detected, such as flags for "outlier" doses and serum levels that fell more than 2 SD from the mean. These were then manually checked for accuracy.

2.1. Predictor analysis

To investigate potential non-AED predictors of ICSEs, we examined 77 variables (Supplementary Table 1), which included various demographics, medical and psychiatric history, and epilepsy-related variables. To evaluate the possible predictors of ICSEs, we first performed univariate analysis using a simple logistic regression model to predict the occurrence of ICSEs. All variables found to be associated with ICSE in the univariate model with an $\alpha \leq 0.1$ level were then fit in the multiple logistic regression analysis using "enter" selection method (with an $\alpha \leq 0.05$). The multiple 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 ICSE. Significance for multiple logistic regression analysis was set at $p < 0.003$ (based on Bonferroni correction of $p = 0.05/17$). The denominator of 17 represents the number of significant variables that were included in the final multiple logistic regression analysis.

2.2. Drug comparison

We investigated the frequency of ICSEs attributed to a newly started AED. We compared the rates of AED-related ICSEs among (a) 1871 patients with AEDs newly started as part of polytherapy, and (b) 1243 patients who were started for the first time on specific AEDs as monotherapy (may or may not be drug naïve at the time of initiation of these AEDs) at our center.

For comparison of rates of ICSEs between AEDs, we performed a series of pairwise χ^2. The rate of ICSEs from one AED was compared with that of another AED in a two-by-two comparison. When χ^2analyses included expected values <5, we used Fisher's exact test. In consideration of multiple pairwise comparisons occurring for each AED, we chose $\alpha = 0.005$ and interpreted the results in terms of consistent patterns seen in the relative rates of intolerable CSEs attributed to the AEDs to avoid Type I error.

We also examined whether the occurrence of ICSEs was related to differences in AED dose load (i.e., dosage). First, AED load was calculated for each individual patient by dividing the AED dose at the time of ICSE by the defined daily dose (DDD) of that particular AED [6]. The DDD is the maintenance dose of an AED used for its main indication in adults considered by the World Health Organization (WHO) [7]. The DDD values are listed in Supplementary Table 8. As an example, the AED load for a patient on 400 mg of medication X at the time of ICSE would be calculated as 400 mg divided by the DDD of medication X. If the DDD was 200 mg, the AED load would equal 2. Then, for each AED, we compared the mean AED load of patients with ICSE with that of patients without ICSE for that particular AED, using one-way analysis of variance (ANOVA).

All analyses were conducted with IBM SPSS Statistics V19 (Chicago, IL).

3. Results

Briefly, the demographics and characteristics of the 2860 patients (Table 1) included a mean age of 40.6 years. The majority of patients (71%) had focal epilepsy. Patients tried an average of 3.5 distinct drug combinations and stayed on an AED for a median duration of 40 months.

Of the entire cohort ($n = 2860$), 428 (15.0%) patients had intolerable CSEs (ICSEs) attributed to at least one AED. Among 1871 patients who were newly started on an AED in polytherapy, 210 patients (11.2%) had ICSEs. Among the 1243 patients who were newly started on an AED in monotherapy, 94 patients (7.6%) had ICSEs. The number of patients who tried each AED, frequency of AED use by epilepsy type, and mean maximum dose for each AED (Table 1) were indicative of the practice pattern at this single site on a group level.

3.1. Predictors of ICSEs

In the univariate analysis comparing the occurrence of ICSE and each independent variable individually, we found significant associations between ICSE and 17 variables (as listed in Table 2).

A multiple logistic regression model was then fit to determine independent non-AED predictors of ICSEs, including all factors that were found to be associated with the outcome with $p < 0.1$ in univariate analysis. To address the issue of multiple comparisons, we set the p value for significance in multivariate analysis at $p < 0.003$ (based on Bonferroni correction), with the p value for "trend" as $0.003 < p < 0.05$ [8]. Intellectual disability (OR = 0.42, $p = 0.001$), and use of AED in polytherapy (OR = 3.41, $p < 0.001$) were found to be significantly associated with ICSEs (with intellectual disability being "protective"), controlling for the other factors in the model (Table 2). All of the variables significant in