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Outcome of treatment changes in patients with drug-resistant chronic epilepsy: A tertiary center experience

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ABSTRACT

Background: Previous studies suggest that changing patients' anti-epileptic drug regimen can reduce the frequency of seizures. The approval of new anti-epileptic drugs with different modes of action during the last decades has provided multiple options for the treatment of epilepsy, although the efficacy of these new drugs is controversial. We aimed to determine the effects of adding or changing to a previously untried anti-epileptic drug, including recently approved drugs, on the frequency of seizures in patients with drug-resistant epilepsy.
Methods: We analyzed treatment changes in drug-resistant patients at our outpatient clinic between 2010 and 2015. We classified patients' frequency of seizures after changes as freedom from seizures, ≥50% reduction, < 50% reduction, no change, increase in seizures < 50% or increase in seizures ≥50%.
Results: We analyzed 189 drug changes in 144 consecutive drug-resistant patients followed up for at least 6 months after the change; 138 changes involved administering newly marketed drugs: lacosamide (n = 65), perampanel (n = 30), eslicarbazepine (n = 29), and retigabine (n = 14). Changes resulted in freedom from seizures in 20 (13.9%) patients and in ≥50% decrease in frequency in 55 (38.2%). The drugs most commonly associated with significant improvement (freedom from seizures or ≥50% reduction) were lacosamide (39.3%), clobazam (11.2%), and levetiracetam (11.2%).
Conclusions: In patients with drug-resistant epilepsy, sequential changes increase the possibility of seizure control, and newer anti-epileptic drugs offer additional options for effective changes. Best combinations must be chosen taking into account drug, epilepsy and patient features.

1. Introduction

Epilepsy is one of the commonest neurological disorders, affecting about 65 million people worldwide (Hirtz et al., 2007). Most patients become seizure free with antiepileptic drugs (AEDs), but up to 30% of patients continue to have debilitating seizures despite antiepileptic drug treatment (Cockerell et al., 1995). Drug-resistant epilepsy has a severe impact on the quality of life and carries an increased risk of sudden unexpected death.

The approval of new AEDs with different modes of action during the past three decades has added multiple options for the treatment of epilepsy (Löscher et al., 2013). Since 1980, third-generation AEDs designed to selectively target a mechanism considered critical for the occurrence of epileptic seizures have expanded the therapeutic options, in particular for patients with drug-resistant epilepsy (Löscher and Schmidt, 1994). These new drugs have other benefits over some older drugs for epilepsy: some avoid inconvenient drug interactions and hypersensitivity reactions, and some are also useful for disorders other than epilepsy (Elger and Schmidt, 2008).

However, studies assessing the efficacy of new AEDs have yielded conflicting results. Some found that the new drugs improve seizure control (Luciano and Shorvon, 2007), but others suggest that most improvements are due to spontaneous remissions rather than to the new drugs (Wang et al., 2013). This suggestion, coupled with information provided by large cohorts of patients followed over long periods (Brodie et al., 2012), has led to the idea that patients who do not respond to initial therapies are unlikely to respond later (Bonnett et al., 2014). If that were certain, sequential trials of new drugs would be of little use in drug-resistant patients.

We aimed to determine the effects of adding or changing to a previously untried antiepileptic drug in patients with drug-resistant epilepsy in clinical practice. We included both classical and recently approved AEDs, provided patients had not tried them before.

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2. Methods

We retrospectively studied patients with drug-resistant epilepsy (Kwan et al., 2009) regularly attended in the outpatient clinic of Hospital Clinic in Barcelona (Spain) between 2010 and 2015 who met the following criteria: age ≥18 years; ongoing seizures despite therapeutic trials with at least two tolerated and appropriately chosen AEDs; prescribed a new antiepileptic drug during the observation period; follow-up ≥6 months after the introduction of the new drug (for those continuing the treatment); and a quantifiable response to the new treatment (i.e., absence of pseudoseizures, no evidence of poor compliance, adequate information provided by patient or family). All patients gave informant consent to use the data for a scientific purpose.

Drug initiation and dose adjustment to reduce the frequency and/or intensity of seizures followed a conventional protocol. A senior neurologist with extensive experience in epilepsy selected the drug and dose according to the type of epilepsy and type of seizures, the patient's clinical context, concomitant medications, and prior history of drug response and tolerability. Following a previously published approach (Luciano and Shorvon, 2007), a drug trial was considered successful, if an improvement lasted for at least 6 months. In that case, the patient was maintained on the drug at the appropriate dose. If a drug trial failed after reaching the maximum tolerated dose, the patient was switched to another drug.

Changes to treatment were classified as additions to the previous treatment or replacement of one of the previous drugs.

We recorded the following clinical information for each patient: age, sex, seizure type, etiology of the epilepsy (structural/metabolic, genetic, or unknown (Berg and Scheffer, 2011)), MRI results, EEG results, age at seizure onset, time from epilepsy onset, number of AEDs tried previously, baseline monthly seizure frequency (number of seizures divided by the period between clinic visits), and seizure frequency while receiving treatment (number of seizures from the time that a stable dose of the new drug was established to the time of the last follow-up, divided by the duration of that period). The number of drugs previously tried was further classified into less than 6 drugs (relative pharmacoresistance) or at least 6 drugs (absolute pharmacoresistance), in accordance with the work of Schiller and Najjar (Schiller and Najjar, 2008).

The main outcome variable was the effect of changing the antiepileptic drug on seizure frequency, determined by comparing the frequencies during the baseline and treatment periods. The effect was classified into six mutually exclusive categories covering the complete range of possible outcomes: a) complete freedom from seizures for at least 6 months, b) ≥50% decrease in seizure frequency (≥50… < 100% reduction of seizure frequency), c) < 50% decrease in seizure frequency, d) unchanged seizure frequency, e) < 50% increase in seizure frequency, and f) ≥50% increase in seizure frequency. We modified this classification from previous works (Cramer and Van Hammée, 2003; Luciano and Shorvon, 2007). We assessed changes after the last follow-up visit without further drug changes. The median follow-up (from time when a stable dose of the new drug was reached to the last follow up or next drug change) was 16 months. We also classified the reasons for discontinuing a new treatment as lack of efficacy, side effects, or both.

We used Student's *t*-test to compare means and Fisher's exact test to compare frequencies; in ordinal variables comparison Mann-Whitney *U* test was performed; we used the Holm-Bonferroni method to adjust p-values for multiple comparisons (Benjamini and Yekutieli, 2001; Holm, 1979; Wright, 1992). Statistical significance was set at $p < 0.05$. We generated a Kaplan-Meier survival curve to estimate the cumulative probability of continuous freedom from seizures. We used IBM SPSS and R version 3.2.5 for all analyses.

Table 1
Demographic and clinical features.

Characteristics	Patients (n = 144)	Drug changes (n = 189)
Mean age (range), years	43 (20–78)	43 (20–78)
Sex (Male/Female)	62/82	74/115
Cause of epilepsy		
Unknown	50	65
Structural/metabolic	89	114
Genetics	5	10
Duration of epilepsy, years		
Mean	26	26
Median	25	25
Range	2–66	2–66
Follow-up in the study, months		
Mean	17	15
Median	14	12
Range	1–69	1–69
Seizure type		
Primary generalized (tonoic-clonic, myoclonic or absences)	15	19
Partial alone	75	96
Partial with generalized tonoic-clonic seizures	54	74
Baseline seizure frequency		
Daily	37	56
Weekly	45	57
Monthly	54	68
Less than Monthly	8	8
Number of drugs previously taken		
Mean	7	7
Range	2–17	2–17

3. Results

We recorded 189 changes to drug therapy involving a previously unused drug in 144 drug-resistant patients (62 (43%) men and 82 (57%) women; mean age, 43 y; range 20–78 y). Table 1 summarizes patients' demographic and clinical characteristics.

Changes to drug therapy consisted in adding a previously unused drug in 100 (53%) cases and replacing a drug with a previously unused drug in 89 (47%). Table 2 reports the changes to drug therapy and the effects of these changes on seizure frequency. Changes involved 12 AEDs; the most common was LCM (34%), followed by PER (16%) and ESL (15%).

A total of 71 (49%) of the 144 patients in whom a previously unused antiepileptic drug was added to or replaced the drug therapy improved substantially after the change: 54 (37.5%) experienced a decrease in seizure frequency ≥50% and 17 (11.8%) became seizure free. The mean follow-up of these two groups of patients after the drug change was 22 months (range 6–61 months). Among the remaining 73 (51%) patients, the frequency of seizures decreased less than 50% in 15 (10.4%) and didńt change in 35 (24.3%). Seven patients had an increase in seizure frequency < 50% and sixteen patients (11.1%) had a significant worsening (seizure frequency increased ≥50%) after the drug. These results are summarized in Fig. 1.

In 39 patients in whom the first change was unsuccessful, a second change resulted in 13 patients (33.3%) experiencing a ≥50% reduction in seizures and 2 (5.1%) becoming seizure free. In 6 patients in whom the first and the second changes were unsuccessful, a third trial resulted in 2 patients (33.3%) experiencing a ≥50% reduction in seizures and 1 patient (16.7%) becoming seizure free. Therefore, in total 20 (13.9%) of the 144 patients were seizure free after taking previously unused AEDs after a mean follow-up of 17 months.

The effect of the 189 drug changes on seizure frequency is shown in supplementary figure 1. In total, 20 changes (10.6%) resulted in