

## Current Literature

In Clinical Science



## The Art of Switching Antiepileptic Medications: Keep Trying or Just Let It Be

### Seizure Recurrence and Remission After Switching Antiepileptic Drugs.

Wang SP, Mintzer S, Skidmore CT, Zhan T, Stuckert E, Nei M, Sperling MR. [Published online ahead of print August 29, 2012, *Epilepsia*. doi: 10.1111/j.1528-1167.2012.03652.x.]

**PURPOSE:** Studies of seizure outcome in patients undergoing serial antiepileptic drug trials have all been uncontrolled, with no account made for the spontaneous changes in disease state that could confound the elucidation of drug effects. In addition, no study has ever looked at outcome following antiepileptic drug switch in seizure-free patients, despite the fact that this is done routinely in clinical practice. We aimed to address both of these issues using a matched case-cohort design. **METHODS:** We followed patients taking phenytoin or carbamazepine in monotherapy for focal epilepsy who were being crossed over to a newer agent as part of studies on the metabolic effects of anticonvulsant therapy. Many had been seizure-free but were being switched nonetheless due to side effects or concerns about long-term adverse consequences. Each patient was matched with two controls of the same seizure status who were taking anticonvulsant monotherapy and whose drug was not switched. Seizure freedom over the ensuing 6 months was the primary end point. **KEY FINDINGS:** There were 43 cases and 86 matched controls. Twenty-three patients (cases) had been seizure-free on their old drug; 5 (21.7%) had seizure recurrence after drug switch compared to 2 (4.3%) of 46 matched controls. Twenty patients (cases) were having seizures on their old drug; 6 (30%) entered remission after drug switch, compared to 8 of 40 matched controls (20%). The two groups differed at baseline in number of anticonvulsants previously failed, which was the most important factor for prognosis. After statistical adjustment to account for this, seizure-free patients had 6.53 times higher odds of seizure recurrence if switched to a new drug (95% confidence interval [CI] 1.02-61.19;  $p = 0.06$ ). Non-seizure-free patients had 1.66 times higher odds of remission if they remained on the same drug compared to switching, although this was not significant (95% CI 0.36-8.42;  $p = 0.532$ ). Neither dose changes, nor drug mechanism, nor duration of seizure freedom had any bearing upon the results. **SIGNIFICANCE:** Although the large majority of seizure-free patients remain so when switched to another agent, about one sixth have a recurrence attributable to the change. Conversely, our study design provides the first evidence to suggest that most improvements in drug-resistant patients are likely due to spontaneous remissions, not new drug introductions. These findings have conflicting implications for two competing models of comparative antiepileptic drug efficacy, which will require further study to elaborate.

### Commentary

The study by Wang et al. raises two very interesting questions: First, what is the risk of switching patients with well-controlled seizures to another medication because of adverse events? Second, is it worthwhile to change medications in patients with uncontrolled seizures, or are we just fooling ourselves with the natural course of the disease?

The study reports that switching phenytoin and carbamazepine to newer agents resulted in recurrent seizures in approximately 20% of patients as compared with 4% with unchanged therapy. This amounts to a six times higher likelihood of recurrent seizures, although this only marginally reaches significance considering all confounding factors in a multiple regression analysis.

The dilemma—the rationale for switching AEDs was to reduce metabolic side effects of older AEDs. Although this is a serious problem, is it worthwhile for the patient to take the risk of recurrent seizures with all of its psychosocial implications (e.g., loss of driving privileges and employment)? An unexpected seizure is the foremost concern of epilepsy patients (1). Seizure recurrence can be costly and detrimental (2). A similar scenario occurs when the patient's seizures are well controlled, but the patient experiences noticeable side effects such as cognitive slowing or psychiatric problems. Patients may be more interested in switching antiepileptic medications if the adverse events are immediately bothersome, but it is certainly more difficult to convince a patient, who has been seizure free and very tolerant of phenytoin or carbamazepine for years, to switch to another agent for cardiovascular consequences that seem far in the future.

Are the newer AEDs as effective as the older AEDs in treating focal seizures? A possible supposition from Wang et

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al. could be that older AEDs are simply more effective, and therefore the recurrence rate is higher when switched over to newer AEDs. This is an unanswered, controversial, and complicated question. Unfortunately, only comparative studies could answer such questions. Our medical system is not set up to fund comparative studies. The only comparative AED study in the United States was performed long before the advent of newer AEDs and showed that carbamazepine and phenytoin were superior to phenobarbital and primidone (3). This is not much help in our current AED environment, but it certainly confirms that phenytoin and carbamazepine are effective. The SANAD study performed in the U.K. is an unblinded study that reported that lamotrigine may, at least, not be inferior to carbamazepine for focal epilepsy (4). However, the study generated a lot of controversy, and reports of shortfalls are multiple (5). Another significant problem is that comparative studies are already outdated before they are published (5). For example, SANAD did not include levetiracetam, which is now preferentially used in many countries.

If we just assume that most AEDs are equally effective, maybe our attention should go to the side-effect profile. However, comparing adverse events of AEDs is even more difficult. What is the weight of cardiovascular risk, sedation, cognition, irritability, psychiatric side effects, headaches, and multiple other adverse reactions? Which ones are more acceptable than others? It seems unreasonable to make generalized statements that specific medications should always or never be used. Therefore, as treating physicians, we attempt to tailor medications to each specific patient.

In the above study, the new AED was titrated up to the full dose before reducing the previous one. What is the right way to switch from one medication to another? With two AEDs, the patient may be experiencing more significant side effects during the titration period but is probably less at risk for seizures. Is tapering one while titrating the other equally safe? Should we more closely assess metabolic interactions between the two AEDs?

The second claim the authors make seems challenging, at first. They suggest that “most improvements in drug-resistant patients are likely due to spontaneous remissions, not new drug introductions.” Their control group with unchanged medications experienced as many seizures as patients whose medications were switched. This basically translates into No matter what we do with AEDs, it does not have any effect. Certainly many patients feel that way. Should we as epileptologists, nevertheless, keep recommending AED changes to our patients? The above study has a strength in using controls compared with many other observational studies, although the controls are not entirely equal to the study patients. We generally seem to ignore the natural history of epilepsy. Spontaneous remissions do certainly occur and may be more frequent than we assume (6). Whether this occurs more frequently in patients with more benign syndromes, and may exclude certain syndromes such as temporal lobe epilepsy, remains unclear (7).

Wang et al. also only address monotherapy. The claim that whatever we do in intractable patients is ineffective seems invalidated by the fact that patients in well-controlled add-on studies of focal epilepsy hardly ever become seizure free in the placebo group, but a small percentage usually achieves seizure

freedom with the active ingredient. However, it could be that epilepsy requiring polytherapy is overall a different clinical syndrome and may not be comparable to the patients studied by Wang et al. The study certainly confirms that once seizures are intractable, however this is defined, then nothing in terms of medication changes is as successful as epilepsy surgery.

The authors elegantly propose two theoretical models about AED efficacy. In the first model, no matter what AED we use, treatment will only be successful in some patients, and patients will be intractable no matter which AED they receive. So, “keep on trying” will be to no avail. Studies that report on early intractability support that model (8). The second model suggests an incomplete overlap in efficacy, so some AEDs may be more effective than others in certain patients or epilepsy syndromes. If the latter is true, we certainly have not done very well in identifying those patients or epilepsy syndromes.

The study has some shortcomings in terms of selection bias, sample size, and confidence intervals. However, it certainly points out some fundamental concepts about AEDs. We, as a community, are called to find more conclusive answers. It also demonstrates that no study can be large enough or inclusive enough to provide us with definitive answers. The conclusion can only be that prescribing AEDs remains an art, weighing all risks and benefits in every particular patient and circumstance. We just need to get better at it.

by Barbara Jobst, MD

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## *Epilepsy Currents Journal*

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