License to Ill: Playing the Odds After Withdrawing and Restarting Antiepileptic Drugs

Seizure Recurrence After Antiepileptic Drug Withdrawal and the Implications for Driving: Further Results >From the MRC Antiepileptic Drug Withdrawal Study and a Systematic Review.

Bonnett LJ, Shukralla A, Tudur-Smith C, Williamson PR, Marson AG. *J Neurol Neurosurg Psychiatry* 2010. doi:10.1136/jnnp.2011.222885 [epub ahead of print].

BACKGROUND: In the UK, patients with epilepsy in remission, who withdraw antiepileptic drug (AED) treatment, are advised not to drive during withdrawal and for 6 months thereafter, assuming the risk of recurrence in the next 12 months is below 20%. Those with a seizure recurrence currently have to be seizure-free for 12 months before returning to drive, whether treatment is restarted or not. New EU regulations recommend returning to driving 3 months after restarting treatment. METHODS: Regression modelling of data from the Medical Research Council AED withdrawal study was undertaken to estimate the risk of seizure recurrence in the next 12 months at various time points following: completion of drug withdrawal; AED reinstatement for those with a recurrence. A systematic review of prospective studies was also undertaken. RESULTS: Immediately following treatment withdrawal, the recurrence risk in the next 12 months was 30% (95% CI 25% to 35%) and at 3 months after withdrawal was 15% (95% CI 10% to 19%). At 3 months following the recommencement of treatment following a seizure recurrence, the risk of a seizure in the next 12 months was 26% (95% CI 17% to 35%), at 6 months 18% (95% CI 10% to 27%) and at 12 months 17% (95% CI 3% to 27%). Systematic review results were similar. CONCLUSION: Current UK legislation concerning time off driving after withdrawing AED treatment may be too conservative. For those restarting treatment after a recurrence, current UK guidance may be too conservative but the new EU guidance too liberal.

Commentary

The job of the epilepsy specialist would be infinitely easier if there were no cars. The automobile, at least in the United States, is such an embedded part of contemporary existence as to be a virtual necessity for most. Thus, the need to drive in the setting of a recent seizure places the interests of the patient in opposition to the public's safety interest. The United Kingdom takes a rational approach, declaring that patients may resume driving under circumstances in which their 12-month seizure recurrence risk is presumed to be below 20 percent. In the United States, on the other hand, we have a hodge-podge of regulations that lend the appearance of having been promulgated by each state's Department of Making Stuff Up.

Further compounding the difficulty is the lack of surrogate markers of the disease process, such that the only way to determine that treatment is still necessary is to go without. Thus, having established over some period of time that seizures are well controlled and driving is reasonable, we then quickly turn to the question of whether treatment can be discontinued, whereupon the same issues vis-à-vis driving once again assert themselves, though this time often without the guide of regulations.

We can certainly all agree that policies of this nature should be data driven, but there has been limited information available regarding rates of seizure recurrence after antiepileptic drug (AED) withdrawal. To fill in this gap, Bonnett and colleagues have gone back to mine data from a study done in the United Kingdom over 20 years ago and applied it to the practical question of when driving should be curtailed and resumed. The study in question involved randomized assignment of patients who were seizure-free for at least 2 years to continued therapy or slow drug withdrawal. The key question addressed in the new analysis is the *time course* of seizure recurrence, embedded within which is the chance of seizure recurrence over the ensuing year after maintaining seizure freedom for a given number of months postwithdrawal.

To this, the authors add two additional pieces of note. The first is a review of the literature for other studies on recurrence after drug withdrawal. The second is a further analysis of *second* seizure risk in the subset of patients who had recurrence following withdrawal and were then restarted on medication. As their literature review attests, no previous study has ever

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addressed this latter group of patients. The attention to this common but understudied circumstance is one of the most valuable aspects of the article.

The top-line results of the study are simple raw percentages, which are seen in the abstract and will not be belabored here. Of particular interest is the literature review, which reveals a fair degree of consistency in the percentage chance of seizure recurrence at various points in time. The studies also show, for the most part, that there is little difference in recurrence rates after 6 months or 12 months of seizure freedom, implying that the imposition of a 1-year driving restriction after a seizure, as is the case in a number of U.S. states and the United Kingdom, is probably unjustifiable. Unfortunately, the differences in study population and design were so numerous as to preclude a formal meta-analysis.

The major strength of the study is its size, with 1,021 patients randomized, yielding 406 of driving age who could be withdrawn from treatment, and 127 in whom AEDs were restarted after a recurrence. The length of follow-up also appears to have been a strength, given that a fair number of patients were followed for as long as 3 years after drug withdrawal, though the authors do not specifically report the mean follow-up duration in the cohort. There are a number of noteworthy limitations relating to the withdrawal process. First, the study protocol called for an extremely slow pace of drug taper, with reductions made every 4 weeks and an explicit aim of having the withdrawal process take at least 6 months. This is an order of magnitude slower than would be typical in the United States, where a clinician would be more likely to withdraw a drug over something like 6 weeks. This limitation is compounded by the second issue, which is that the precise schedule of drug withdrawal was not known for each patient, so that the authors were obliged to assume that taper had taken place over exactly 6 months; this effectively renders all of their data an approximation. Third, and most important, the authors excluded from the analysis all patients who had a seizure *during* the withdrawal process. This was presumably done with an eye toward practical application to driving laws, with the thought that no patient would be driving during the period of drug taper anyway. While this seems a fair assumption, the exclusion of this group may have materially altered the authors' data on the incidence and timing of recurrent seizures after AED reinitiation. All of these factors may limit the generalizability of their findings to some extent.

The authors apply this data to driving regulations in the United Kingdom and the European Union, where health-related decisions are designed to make sense. How, then, to apply this to the fragmentary world of the United States? One possible use would be to petition the authorities in various states to implement driving restrictions that are reasonable and evidence based. A second application would be in those states without fast guidelines in which the seizure-free interval is left to the physician's discretion; those physicians now have an evidentiary guide. A third and important application is to the issue of resumption of driving after resumption of treatment, a problem which seems to be addressed by few, if any, U.S. states, leaving the matter wholly to the physician. The news in this regard is not good, as the 12-month recurrence rates—26% after 3 months of resumed treatment, and 17% even after a year of resumed treatment—are higher than might have been anticipated.

But in the end, all of this really just points up the foolishness of asking physicians to make driving judgments. We are duty bound to act in the interests of our patients, not of the rest of the universe. When our professional obligation to the patient is in conflict with the interests of society at large, the questions at hand are much larger than medicine, and it is within neither our purview nor our expertise to weigh such interests against each other. Far better to have these decisions made by governing bodies who are accountable to all constituents than to put physicians in a position of making global decisions about risk and safety. We can only hope that this study and others of its ilk will be put to use in designing laws that appropriately balance rights, welfare, and utility.

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