

What Test is Needed to Discontinue Medications after Successful Epilepsy Surgery?

Can J Neurol Sci. 2014; 41: 405-406

Owing to its excellent efficacy and safety profile, resective surgery has become a prime therapeutic consideration for refractory lesional epilepsies. A wealth of evidence, experience, and outcome data has established the foundational role for epilepsy surgery by clarifying clinical application, patient selection, and generating refinements in surgical techniques.¹ In their paper, Harroud *and colleagues*² attempt to tackle a prescient question. The authors critically reviewed the literature to determine if specific tests such as electroencephalogram (EEG), magnetic resonance imaging (MRI) or anti-epileptic drug (AED) serum levels reliably predict discontinuation of AEDs after successful epilepsy surgery, and if so, could such testing be useful in prognosticating the main, worrisome outcome following AED withdrawal, which is seizure relapse.

The elucidation of what testing can accurately predict seizure relapse after post-surgical AED discontinuation is a question that has not been adequately addressed in the literature. In the study of Harroud *et al*², seven studies met inclusion criteria, five of which were retrospective and none of which were randomized or controlled. Four studies found no association between the presence of interictal epileptiform discharges on EEG and risk of seizure recurrence, while three did. The authors further concede that there is no evidence regarding the utility of post-operative AED serum levels or neuroimaging in predicting the risk of seizure recurrence following AED tapering. The lack of proven efficacy surrounding three easily accessible and potentially synergistic biomarkers - neuroimaging, AED levels, and EEG patterns - is bound to frustrate clinicians.

The literature demonstrates that few patients after successful epilepsy surgery never regain a seizure-free state following AED reduction (after successful epilepsy surgery most patients maintain seizure-free state following AED reduction).^{3,4} However, the majority of patients tend to tolerate AED tapering quite well.^{3,4} While this knowledge is superficially reassuring, it is an inadequate basis for clinical decision-making. Schmidt *et al*³ reviewed temporal lobe surgery outcomes and concluded that one third of patients were cured, one third were controlled on AEDs, and one third continued to have disabling seizures on AEDs. The authors acknowledged the retrospective, unblinded and uncontrolled nature of the included studies, short follow-up period (<5 years), contradictory findings, and focus on temporal lobe epilepsy as major limitations that impede translation of underlying study results to clinical practice.

Schiller *et al*⁵ retrospectively determined that in patients who discontinued AEDs post-surgery, seizures recurred in 26% at five years, compared with 7% of those who did not discontinue AEDs. It should be kept in mind, however, that a substantial

proportion of post-surgical patients relapse after achieving remission, and not all of the risk can be ascribed to AED cessation.^{4,6,7} Retrospective studies suggest an increased rate of seizure-recurrence with earlier (≤ 9 month post-surgery) post-operative AED withdrawal—the rate of seizure recurrence is up to 20% higher in the earlier withdrawal category. It is encouraging to note, however, that should seizures occur in the context of AED discontinuation, seizure control is regained in 50-70% of patients.⁸

In their prospective evaluation, Berg *et al*⁴ concluded that seizures recurred in 32% of those who decreased or stopped AEDs and in 45% of those who did not, a statistically significant difference. It remains unclear if the act of reducing AEDs worsens the prognosis for these patients as long-term follow-up data are lacking. In a recent meta-analysis⁹, only 16% of temporal lobe surgery patients and 18% of those undergoing all types of surgery were cured. The percentage of cured patients was lower than in short-term studies which variously cite remission rates of 25% in adults and 31% in children⁵. The lower proportion of optimum outcomes in this meta-analysis is explained by the more stringent selection criteria that included only studies with >5 years of follow-up.⁹ There is consistent evidence that early AED and seizure post-operative outcomes tend to decline over time.⁹ The inverse association between duration of follow-up and poorer seizure outcomes in patients discontinuing AEDs is evident in this meta-analysis and other recent studies.^{9,10}

Unfortunately, the utility of various clinical and para-clinical predictors that one would intuitively consider to be helpful is far from certain. One controlled study found that AED discontinuation had no impact on seizure remission, and factors such as persistent auras, use of intracranial EEG, type of lesion or location of resection did not affect seizure outcomes after discontinuing AEDs.⁴ Our nationwide survey of Canadian epileptologists confirmed that clinical judgement with respect to post-operative AED withdrawal is informed by a mix of patient preference, local practice patterns, and personal biases. It is also influenced by expert opinion and prevailing trends. This study further confirmed that epileptologists operate under the precautionary principle. Epileptologists considered a good candidate for AED cessation being one who has focal pathology, is completely seizure-free, has an anterior temporal lobe resection with complete resection of seizure focus, a normal EEG before reduction, the presence of unilateral mesial temporal sclerosis on MRI or histopathology, and no epileptiform discharges on post-operative EEG. The factors cited against AED reduction were patient desire to resume driving, focal

paroxysmal activity on EEG after surgery, generalized epileptiform activity on EEG, and persistent isolated auras and any seizures after hospital discharge.¹⁰ These findings complement US survey results, suggesting that North-American epileptologists have arrived at an informal consensus.^{11,12}

Harroud *et al*² serve a timely reminder that further research is urgently needed if the state of prognostication is to advance beyond speculation. It is sobering to consider that we lack an empirical basis by which to decide if and when AEDs can be withdrawn safely post-surgery, and more importantly, in whom doing so would be dangerous. A trend towards earlier surgical resection with the ensuing prospect of seizure freedom is taking hold and it behooves us all to define a rational framework to guide pharmacological therapy.

DISCLOSURES

Dr. Téllez receives grants from the University of Saskatchewan, UCB Canada and the Royal University Hospital Foundation, Saskatoon, Saskatchewan, through the Mudjatik Thyssen Mining Professorship in Neurosciences.

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