

Current Literature

In Clinical Science



Medication Management After Epilepsy Surgery: Opinions Versus Facts

Timing of Antiepileptic Drug Withdrawal and Long-Term Seizure Outcome After Paediatric Epilepsy Surgery (TimeToStop): A Retrospective Observational Study.

Boshuisen K, Arzimanoglou A, Cross JH, Uiterwaal CS, Polster T, vanNieuwenhuizen O, Braun KP; TimeToStop Study Group. *Lancet Neurol* 2012;11:784–791.

BACKGROUND: Postoperative antiepileptic drug (AED) withdrawal practices remain debatable and little is known about the optimum timing. We hypothesised that early AED withdrawal does not affect long-term seizure outcome but allows identification of incomplete surgical success earlier than late withdrawal. We aimed to assess the relation between timing of AED withdrawal and subsequent seizure recurrence and long-term seizure outcome. **METHODS:** TimeToStop included patients aged under 18 years from 15 centres in Europe who underwent surgery between Jan 1, 2000, and Oct 1, 2008, had at least 1 year of postoperative follow-up, and who started AED reduction after having reached postoperative seizure freedom. Time intervals from surgery to start of AED reduction (TTR) and complete discontinuation (TTD) were studied in relation to seizure recurrence during or after AED withdrawal, seizure freedom for at least 1 year, and cure (defined as being seizure free and off AEDs for at least 1 year) at latest follow-up. Cox proportional hazards regression models were adjusted for identified predictors of timing intervals. **FINDINGS:** TimeToStop included 766 children. Median TTR and TTD were 12.5 months (95% CI 11.9–13.2) and 28.8 months (27.4–30.2), respectively. 95 children had seizure recurrence during or after AED withdrawal. Shorter time intervals predicted seizure recurrence (hazard ratio [HR] 0.94, 95% CI 0.89–1.00, $p=0.05$ for TTR; and 0.90, 0.83–0.98, $p=0.02$ for TTD). After a mean postoperative follow-up of 61.6 months (SD 29.7), 728 patients were seizure free for at least 1 year. TTR and TTD were not related to regain of seizure freedom after restart of drug treatment (HR 0.98, 95% CI 0.92–1.05, $p=0.62$; and 0.93, 0.83–1.05, $p=0.26$, respectively), or to seizure freedom (0.97, 0.89–1.07, $p=0.55$; and 1.03, 0.93–1.14, $p=0.55$, respectively) or cure (0.97, 0.97–1.03, $p=0.84$; and 0.98, 0.94–1.02, $p=0.31$, respectively) at final follow-up. **SIGNIFICANCE:** Early AED withdrawal does not affect long-term seizure outcome or cure. It might unmask incomplete surgical success sooner, identifying children who need continuous drug treatment and preventing unnecessary continuation of AEDs in others. A prospective randomised trial is needed to study the possible cognitive effects and confirm the safety of early AED withdrawal after epilepsy surgery in children.

Commentary

Antiepileptic drug (AED) discontinuation after surgery is a very polarizing issue. The driving forces on either end of the debate are obvious: discontinuing AEDs could eliminate unnecessary side effects, improve quality of life, and reduce cost, while maintaining AEDs could avoid potential risks of breakthrough seizures and their untoward consequences. Every epileptologist “believes” in an ideal candidate patient population, in a best time to initiate AED withdrawal—if at all—and in an optimal rate of medication tapering. Every “believer” can provide *logical reasons* supporting his/her stance. But, like every “belief,” the current practice of postoperative medication management is closer to faith and personal experience than it

is to solid evidence. Multiple retrospective series are available (1–7), but few prospective studies have attempted to evaluate this issue, and both were observational (8, 9). In this “evidence-scant” environment, what do we know?

First, several retrospective studies suggest an increased rate of seizure-recurrence with earlier postoperative AED withdrawal (3, 6–7): when “earlier” was defined as less than 6 months (3) or 9 months (7) after surgery, the rate of seizure recurrence was an absolute 15 to 20 percent higher in the earlier withdrawal category. The article by Boshuisen et al. chosen for this commentary further quantifies this hazard to an additional 5% recurrence risk for every 3 months reduction in the time interval from surgery to the start of AED withdrawal. Yet, the two prospective series do not necessarily support this concern, as one found similar relapse rates between patients who continued their AEDs and those who reduced them either from two to one AED or from one to no AED (8). The other reported on the rates of seizure recurrence after AED taper initiated at 3

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months or 1 year after surgery, with an eventual rate of seizure recurrence similar to historical controls (9). So, the debate about the immediate implications of AED withdrawal on seizure control can continue.

Second, most studies agree that seizure recurrences starting in the setting of AED withdrawal are easier to control than unprovoked postoperative seizure relapses (10). In Boshuisen et al., 70% of patients whose seizures started with AED reduction or discontinuation eventually regained seizure control, in concordance with prior data reporting remission rates of 50 to 66 percent in this scenario (7, 8, 10). While definitely encouraging, here are the issues with these numbers: 1) the significance of a 30% risk of being unable to regain seizure control after stopping AEDs is different for a child facing the prospect of a lifetime of cognitive and other medication side effects versus an adult who has finally regained independence, driving privileges, and a chance for meaningful employment; 2) it remains difficult to counsel an individual patient about the potential consequences of an AED withdrawal seizure because we don't really know how easy or difficult it will be to re-achieve seizure control even if he/she is among the lucky 70% (i.e., is this control achieved over weeks or months, by returning to the preoperative AED regimen or necessitating additional AEDs).

Third, none of the studies to date demonstrated any negative long-term implications on seizure outcomes in patients who attempted AED withdrawal. While earlier studies found similar long-term seizure outcomes in patients whose medications were withdrawn compared with those who continued their AEDs (8), Boshuisen et al. further show here that these long-term seizure outcomes were independent of the time to start or complete AED withdrawal.

The overarching suggestion from all these findings is that withdrawing AEDs may uncover an incomplete resection of the epileptic focus (or possibly a resection that converted epilepsy from a pharmacoresistant to a pharmacoresponsive disease) without damaging the patient's long-term prospects at seizure-freedom, no matter how early this withdrawal challenge is attempted. In other words, AED withdrawal may be to postsurgical epilepsy what a cardiac "stress test" is to coronary artery disease: rather than "causing" myocardial infarction, it serves to screen for its underlying pathology and to identify it early. If correct, this hypothesis would limit the uncertainty about whether, when, and how to withdraw AEDs after successful surgery, and would actually be a welcome tool to confirm who was cured with surgery and who needs to continue medical therapy. In reality, however, despite all the knowledge and hypotheses summarized above, the clinical practice of postoperative AED management hasn't changed much over the past 2 decades (11, 12). Why? Because no matter how attractive the "stress test" hypothesis is, and how much circumstantial evidence supports it, it remains essentially unproven. Let's revisit the evidence and discuss the challenges.

First, seizures recur after surgery, whether patients are taking AEDs or not. In fact, less than 20% of all postoperative seizure recurrences start in the setting of AED withdrawal (10). Second, approximately half of all postoperative seizure recurrences manifest first within 6 months after surgery, with slower subsequent rates of seizure recurrences such that *any* patient, whether on AEDs or not, will have higher rates of subsequent

seizure recurrences earlier after surgery than *any* patient (on or off AEDs) who has already achieved a longer period of remission. Taken together, these two facts highlight the fine line between association and causality and represent the main limitation of drawing any "alarming" conclusions on the immediate implications of AED withdrawal on seizure control using the retrospective or observational prospective data currently available: we don't really know how many of the seizure recurrences occurring after early or late AED withdrawal would have happened anyway, even if AEDs were continued. In fact, the nonrandomized and noncontrolled cohorts reported to date represent, by definition, a biased sample in which both physicians and patients felt comfortable enough to attempt AED withdrawal (typically after at least 1 to 2 years from surgery). These selected cohorts ultimately had low overall rates of seizure relapses (12% in Boshuisen et al., for example) underpowering any meaningful noninferiority analyses, and ironically then compromising "reassuring" conclusions about the long-term safety of attempting AED withdrawal.

In summary, the "stress test" hypothesis may be correct, but until it is unequivocally proven, the current situation of clinical equipoise will continue, and thoughtful retrospective studies like the manuscript at hand will be precious contributions. This commentary will not be the first call for a randomized clinical trial (RCT) to resolve these challenging questions, and while the research funding agencies contemplate the financial cost of such an RCT, patients and society will continue paying the exponentially bigger financial and psychosocial costs of unnecessary AED polytherapy and its complications.

by Lara Jehi, M.D.

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