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Debate: Should antiepileptic drugs be stopped after successful epilepsy surgery?

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Summary

There is no consensus on whether or when to stop anticonvulsant drug treatment in patients after apparently successful epilepsy surgery. Although there are compelling reasons to consider antiepileptic drug (AED) discontinuation, there are relatively few data, and no class I data, to guide patient and physician decision-making on this topic. This debate lays out a conceptual framework for considering the issue of AED discontinuation, and reviews and critiques the avaialble data. The goal is to provide physicians with the best available data, a context in which to consider it, and a full understanding of its limitations. This article also highlights an area that is ripe for further prospective study.

KEY WORDS: Epilepsy surgery, Outcome, Anticonvulsant Drugs, Discontinuation, Evidence-based medicine, Risk stratification.

Pro: The Case For Discontinuing AEDs Andrew J. Cole

There are no prospective randomized data and limited prospective and retrospective data to guide neurologists in evaluating the utility and adverse consequences of continuing antiepileptic drug (AED) treatment after epilepsy surgery. AED treatment is routinely continued after epilepsy surgery for a minimum of 1–2 years, and often indefinitely. There is no consensus on either dose reduction or simplification during the first 2 years, and discontinuation after 2 years. Moreover, in the absence of data, patient preferences and physician practices vary widely. Herein we seek to provide an intellectual framework for considering this issue. For the purposes of this discussion, we will restrict our focus to patients who have had no seizures since epilepsy surgery or only seizures during the acute perioperative period. Such patients would typically be classified as having an Engel class IA outcome (Engel et al., 1993, pp. 615).

Plausible reasons not to stop AED treatment after epilepsy surgery include the possibility of an increased risk of breakthrough seizures, the potential psychosocial damage of even a single event, the concern that even a single event could promote the recurrence of refractory seizures, and the conventional conservative notion that ''If it ain't broke, don't fix it.'' At the same time, there are legitimate reasons to endeavor to stop AED treatment after apparently successful epilepsy surgery, including the desire to avoid unnecessary long-term toxicities; to eliminate ongoing cognitive adverse effects of medications; to reduce costs associated with medication, monitoring, and follow-up care; and to remove daily treatment that serves as a major affirmation of the ''sick role.''

Conceptually, our consideration of the question should be guided by the same considerations that govern analysis of all prophylactic treatments such as vaccination, perioperative antibiotic therapy, or treatment of hypertension and hypercholesterolemia. These considerations are listed in Table 1. In the following discussion we will consider the data available to address each of these issues with regard to postoperative recurrent seizures.

What Is The Incidence of RecurRent Seizures After Apparently Successful Epilepsy Surgery?

The long-term outcome of epilepsy surgery has been studied prospectively and retrospectively in an unblinded fashion by several groups. Yoon et al. (2003)studied 175 patients who were initially seizure-free for 1 year after

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Table 1. Prophylaxis: Should you treat 100% of a population in whom only a fraction are destined to have the event you are trying to prevent?

What is the incidence of the event you are trying to prevent?
Is it possible to stratify the risk of occurrence of the event of interest?
What is the seriousness of the event you are trying to prevent?
What is the likelihood that prophylaxis will prevent the event of interest?
What is the risk of prophylaxis?

resective epilepsy surgery. In this population the likelihood of seizure freedom declined from 83–56% as duration of follow-up increased from 3–10 years. McIntosh et al. (2004) studied 325 patients who underwent temporal lobectomy and found that the probability of complete seizure freedom declined from 55–41% as follow-up continued from 2–10 years. Of those who were seizure free for 2 years after surgery, 74% remained seizure free at postoperative year 10, and complete discontinuation of anticonvulsant drugs after 2 seizure-free years was not associated with an increased risk of recurrence. Tanriverdi et al. (2008) found that 70% of patients were seizure-free 12 years after surgery for temporal lobe epilepsy. Engel surveyed multiple epilepsy centers and found that the likelihood of complete seizure freedom depended on the type of resective surgery performed. Whereas there was no difference in outcome between anterior temporal lobectomy and amygdalohippocampectomy (as confirmed by Tanriverdi et al. [2008]), patients who underwent neocortical resections or multilobar resections did substantially worse (Engel et al., 1993). Berg et al. (2006) studied 301 patients, 129 of whom reduced or discontinued medication after at least 1 year of seizure freedom and found no significant difference in the rate of seizure recurrence (32% in the drug-reduction group and 45% in the drug-continuation group). Taken together, these studies suggest a risk of recurrence ranging from 25–50% over 10 years in patients who are initially seizure free, and suggest that the chances of remaining seizure-free are not significantly affected by whether or not AEDs are discontinued.

Is It Possible to Stratify the Risk of Occurrence of Recurrent Seizures after Apparently Successful Epilepsy Surgery?

Several groups have used unblinded, generally retrospective analysis to examine risk factors for seizure recurrence. McIntosh et al. (2004) found that patients with foreign tissue lesions or hippocampal sclerosis were much more likely to remain seizure-free than those with no, other, or distant pathologies (using all available evidence, including imaging, to assign a presumed pathological diagnosis). Additional univariate analysis suggested that longer duration of epilepsy, later age at surgery, and the presence of secondarily generalized seizures each increased risk of recurrence, whereas with use of a multivariate analysis adjusting for pathology, only the occurrence of preoperative secondarily generalized seizures conferred an increased risk of recurrence. These investigators also examined a cohort with late recurrence (>2 years after surgery) and found no specific risk factors, including AED discontinuation, for late recurrence (McIntosh et al., 2004). Similarly, Yoon et al. (2003) found that only longer duration of epilepsy and absence of pathologic findings predicted higher risk of recurrence. Berg et al. (2006) found no difference in recurrence rates between those who eliminated or continued AEDs. Among those who eliminated AEDs, delayed remission after hospital discharge was associated with an increased risk of relapse. Interestingly, neither postoperative electroencephalography (EEG) nor post-AED discontinuation EEG has been examined as a potential predictor of recurrence. Taken together, these studies suggest that, with the exception of lack of pathologic findings, physicians do not have robust tools available to stratify risk of recurrence. We note, however, that EEG, which is widely used to estimate risk recurrence after first seizure and to make medication discontinuation decisions in medically treated patients, has not been adequately studied in patients after epilepsy surgery.

What Is the Seriousness of Recurrent Seizures after Apparently Successful Epilepsy Surgery?

Recurrent seizure after epilepsy surgery may be inconvenient, disappointing, disruptive, or dangerous. Little more than anecdotal data is available to quantify the relative "seriousness" of recurrent seizure. At the very least, recurrence must be inconvenient, disappointing, and disruptive. There is little evidence that isolated seizures carry a substantial risk of injury or death, especially in patients who have typically had hundreds to thousands of seizures during their lifetimes, although patients who have been seizure-free after surgery are more likely to have resumed an active lifestyle, including driving, and, therefore, may be at modestly elevated risk. Psychological harm resulting from seizure recurrence is difficult to quantify. Tanriverdi et al. (2008) found that whereas most patients had an improved quality of life after epilepsy surgery, those that were seizure-free had a greater improvement. Similarly Langfitt et al. (2007) reported

that quality of life improved after successful epilepsy surgery, but remained stable or declined in patients not in remission, depending on whether they had postoperative memory decline. Blumer et al. (1998) analyzed psychiatric outcome after epilepsy surgery in 50 patients and noted that de novo depression occurred in 6 patients who experienced recurrent seizures, suggesting that recurrence may have important psychological consequences in some patients. Finally, although some patients and physicians fear that seizure recurrence after epilepsy surgery and medication discontinuation will predispose to the recurrence of medically intractable epilepsy, there is simply no evidence that this is the case (Yoon et al., 2003; McIntosh et al., 2004; Berg et al., 2006). Together, these studies support the notion that although seizure recurrence in the setting of medication discontinuation after epilepsy surgery may cause anxiety and depression for some patients, it is unlikely to cause major physical harm or increase the risk of recurrent refractory epilepsy.

What Is the Likelihood That Prophylaxis Will Prevent Recurrent Seizures after Apparently Successful Epilepsy Surgery?

There are no robust data on the efficacy of anticonvulsant treatment in the setting of recurrent seizures after medication discontinuation and seizure recurrence after epilepsy surgery. Logically, however, it seems unlikely that medication would lead to seizure freedom at a higher rate in this group of patients than in the general epilepsy population, so it might be reasonable to estimate no greater than a 70% efficacy rate. No studies of epilepsy surgery patients with an initial good response to surgery found that continuation or discontinuation of AEDs had a meaningful effect on risk of recurrence; therefore, it is difficult to conclude that ongoing treatment is particularly effective as a prophylactic measure.

What Are the Risks of Prophylaxis?

The ongoing use of anticonvulsant drugs carries the risks of continued adverse events, including cognitive and central nervous system (CNS)–related side effects and the continued exposure to the long-term adverse health effects of AED treatment, including cosmetic, metabolic, and reproductive side effects as well a drug–drug interactions. Continued treatment imposes an ongoing cost as well as a requirement for medical and laboratory monitoring. Finally, there is at least a theoretical concern that ongoing treatment provides a constant affirmation of the ''sick'' role and may interfere with vocational and psychosocial rehabilitation. Simply said, no reasonable person would volunteer to take centrally active medication on a chronic basis unless there was a substantial expectation of benefit.

Table 2. Theoretical calculations of utility of continued AED treatment after apparently successful epilepsy surgery

	Best case (%)	Intermediate case (%)	Worst case (%)
Risk of recurrence	20	50	50
Success of prophylaxis	70	70	50
Fraction of patients to benefit	14	35	25
Fraction of patients needlessly/ineffectively treated	86	65	75

Conclusions

In the preceding discussion we have noted that risk of seizure recurrence after apparently successful epilepsy surgery, although substantial, is largely unpredictable and occurs in only a minority of patients. Except for the presence of absence of specific pathologies, there are no robust tools to stratify risk in most cases, and perhaps the tool most likely to be useful, EEG, has not been adequately studied. The consequences of recurrent seizures that occur in the setting of medication discontinuation are likely to be modest. The success of prophylaxis is limited, and it carries significant risks. In Table 2 we endeavor to present worst, intermediate, and best case scenarios to emphasize that many patients would be treated needlessly or ineffectively under a universal policy of indefinite medical treatment after epilepsy surgery. We conclude that although new data are required, especially about the utility of EEG in risk stratification, with our present knowledge, attempts to discontinue treatment after a period of sustained seizure freedom should be encouraged.

Con: The Case against Discontinuing AEDs
Samuel Wiebe

The argument in perspective

Consider a gathering of clinicians from different centers involved in epilepsy surgery, having a dialogue about AED discontinuation in patients who are seizure free following epilepsy surgery. Different clinical scenarios are presented, and management is discussed. Some clinicians tentatively express a level of uncertainty about when, in whom, and how rapidly to discontinue AEDs, and what information to give the patient. Others, however, speak with conviction, disagreement

emerges, and the discussion becomes polarized. Most participants become vehement proponents or opponents of various courses of action, expressing their beliefs with increasing certainty and passion. What is the evidence for such beliefs?

A recent survey of practice patterns in epilepsy centers in the United States would support the description of the preceding exchange. In that survey, 98% of clinicians would not discontinue AEDs earlier than one year after successful surgery, and 62% would only stop them after 2 years (Berg et al., 2007).

That clinicians and patients aim at discontinuing AEDs after successful surgery makes clinical sense for several reasons. First, neither clinicians nor patients wish to undertake unnecessary treatment. Second, side effects of AEDs are common, may be unrecognized, and have broad-ranging consequences, including a negative impact on quality of life (Gilliam et al., 2004; Gilliam, 2002). Third, many patients expect to discontinue AEDs after successful surgery. Pilot data from an epilepsy surgery randomized controlled trial (RCT) demonstrate that 90% of patients believe that surgery will render them medication free, and after extensive education 60% still held this belief. Fourth, clinicians harbor the hope that patients will be cured by surgery, and that if cured they will be able to discontinue AEDs. However, the logic to support AED reduction and discontinuation in seizure-free patients would have to consider one or more of the following premises: (1) surgery removes the seizure producing cortex in its entirety; and (2) these patients do not have an inherent tendency to have seizures, or surgery changed the brain in such a way that tendency was removed. Clearly, there is enormous variability in these factors, and they may be impossible to determine a priori; therefore, they are difficult to support.

Why do clinicians believe that it is necessary to wait at least 2 years before reducing AEDs and that reduction should be slow? For unknown reasons a notion has developed that waiting to decrease or withdraw AEDs improves the chance of remaining seizure free. The presumed logic supporting this notion would require consideration of one or more of the following premises: (1) AEDs have an antiepileptic effect that needs some time to take effect after surgery; (2) longer waits increase our certainty that surgery has abolished epileptogenesis; (3) we do not know a priori who will be cured, and a longer period of seizure freedom on AEDs is the best indicator of a complete cure of epilepsy. It is transparent that there is little evidence to support any of these premises. Therefore, one could equally support a policy of early or immediate AED discontinuation after surgery. Arguably, this could promptly identify patients who are not cured and in whom rapid reinstitution of AEDs is required. However, there has not been a strong voice supporting such a view.

Table 3. Hierarchy of evidence about therapeutic interventions

Type of study (from strongest to weakest)
1. Randomized controlled trials
2. Nonrandomized, controlled trials
3. Cohort studies with no controls
4. Case series
5. Anecdotes

Table 4. Evidence classification used by the American Academy of Neurology (AAN)

Class of evidence	Criteria
I	RCT with masked outcome assessment
II	RCT with unmasked outcome assessment, or non-RCT with matched controls and masked outcome
III	Non-RCT, with no matched controls, and unmasked outcome assessment
IV	Case series and all other studies not fulfilling the preceding criteria

RCT, randomized controlled trial.

Making clinical decisions

Seasoned clinicians recognize two guiding principles in making decisions about the management of individual patients: (1) evidence informs clinical decisions; and (2) there is a hierarchy of evidence, which is dictated by its scientific validity and applicability (Table 3).

Numerous organizations including the American Epilepsy Society (AES) and the American Academy of Neurology (AAN) have developed a formal process for assessing the quality and hierarchy of the evidence. This allows organizations to stipulate the strength of clinical recommendations that the evidence can afford. Over the years, the AAN has developed a well-defined system for assessing the quality of evidence, in which each study is assigned a class of evidence ranging from I to IV (best to worst) (Table 4).

Based on this hierarchy, the AAN grades its recommendations for clinical practice into four categories of certainty (Table 5). Accordingly, class I evidence supports definitive practice recommendations, whereas low quality evidence (class IV) cannot support any recommendations about clinical decisions. This system has been used to assemble numerous practice recommendations in the area of epilepsy, including epilepsy surgery (Engel et al., 2003), AEDs (French et al., 2004a, 2004b), and management of the first seizures (Krumholz et al., 2007). We will assess the quality of the evidence about AED withdrawal using this well-known hierarchical framework.

Table 5. Evidence and recommendations

Strength of evidence support	Strength of recommendation	Evidence requirement—number and type of study
Definitive	"Should do"	2 Class I
Probable	"Should consider"	1 Class I, or 2 Class II
Possible	"May consider"	1 Class II, or 2 Class III
Unknown	"No recommendation"	Any Class IV

What Is the Evidence for AED Discontinuation after Epilepsy Surgery?

A systematic review and critical appraisal of the literature dealing with AED discontinuation or reduction after epilepsy surgery is revealing.

A literature search identified seven studies describing outcomes for at least 5 years in 740 patients who underwent planned AED withdrawal after epilepsy surgery (Sironi et al., 1983; Schiller et al., 2000; Berg et al., 2006; van Veelen et al., 2001; Al-Kaylani & Abou-Khalil, 2002; Lachhawani et al., 2008). Five studies described AED withdrawal, one described AED reduction, and one studied focused on children. AEDs were withdrawn in 71% of adult patients and 52% of children. Seizures recurred in 34% patients. All studies except that of Berg et al. (2006) were retrospective and had no controls, and none of the studies had blinded outcome assessment. Because all studies in this category were class IV, no clinical practice recommendation can be supported at all.

Tellez-Zenteno et al. (2007) focused a systematic review of AED withdrawal on studies with long-term (>5 years) follow-up. They identified 12 studies fulfilling minimum methodologic criteria. In the long term, 33% of patients were on AED polytherapy, 39% were on AED monotherapy, and 25% were on no AEDs. Nine studies involving 932 patients reported on the number of patients who were cured (off AEDs and seizure free). Overall 22% of patients were in this category. However, an analysis of the scientific quality is sobering. All of the studies were retrospective case series without controls and without blinding of outcomes and were, therefore, class IV and unsuitable to support any clinical practice recommendations.

Tellez-Zenteno et al. also identified four controlled studies that explored AED discontinuation 5 years or longer after epilepsy surgery (Guldvog et al., 1991; Vickrey et al., 1995; Altshuler et al., 1999; Helmstaedter et al., 2003). Yet only one study is prospective, and none of the studies have an independent or blinded assessment of outcomes. Again, these are all class IV studies on which no clinical practice recommendations can be based.

In summary, the best available evidence regarding reduction or discontinuation of AEDs after epilepsy surgery consists of 24 class IV studies, which cannot support any clinical practice recommendations.

Does AED Withdrawal Influence Seizure Recurrence after Epilepsy Surgery?

One study in particular has addressed this question. Berg et al. (2006) performed a multivariate analysis of the factors that predicted achieving a 1-year seizure-free period after epilepsy surgery in a cohort of 291 patients, of whom 129 reduced or discontinued AEDs. Among these patients, 41% relapsed and 37% did not regain control. As in other surgical series, 30% were seizure free and off AEDs (cured). Surprisingly, these authors found no association between AED reduction or discontinuation and seizure outcome. Instead, it was the occurrence of early postoperative seizures that predicted seizure outcome. There was no effect of type of lesion, persistence of auras, use of intracranial monitoring, or pathologic diagnosis. This study illustrates how little we know about the role of AEDs following surgery in seizure-free patients, and about the importance of other factors.

Conclusions

Evidence-based medicine refers to applying the best available evidence to the management of individual patients. If it existed, adequate evidence could support a recommendation to either continue or stop AEDs after successful surgery. However, the evidence is insufficient to support a clinical recommendation for two reasons. First, it is a reflection of what is done and not of what should be optimally done. Second, the studies are methodologically very weak (class IV), and insufficient to derive solid clinical inferences. There can hardly be a clinical argument against attempting to decrease and eventually discontinue AEDs in seizure-free patients following surgery. However, a strong case can be made against using the existing limited evidence to inform our future practice, and against accepting prevailing regional practice patterns as the standard of care.

Even in the absence of evidence to guide clinical practice, clinicians faced with the decision to discontinue AEDs in seizure-free patients will have to consider the potential risks of AED discontinuation and weigh these against the expected benefits. These risks include, on the one hand, the clinical, social, and psychological consequences of recurrent seizures, and on the other, the small but important probability that restarting AEDs may no longer control seizures.

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