

Postsurgical Treatment of Epilepsy

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In people with localization-related epilepsy who do not respond well to medication and continue to have seizures despite having been evaluated and treated by an epilepsy specialist, current recommendations are to consider surgery as an alternative to continued trials of different antiepileptic drugs (AEDs).

There is a growing trend to pursue surgery earlier in the course of the seizure disorder than has been the practice in the past (1–3). This shift is occurring because few if any patients whose seizures are not controlled after trials with the first two or three appropriate AEDs are likely to benefit from trials of additional AEDs, either individually or in combination. This appears to be true despite the recent proliferation over the past decade of several new drugs. In addition, the toll that uncontrolled seizures take on the individual and the family is cumulative, and the years lost to uncontrolled seizures cannot be recaptured (4). Whether the effects can be reversed is not clear. Last but not least, by any means, continued concerns exist about the side effects, especially cumulative, of taking AEDs over a period of many years. People considering surgery have, as their top concerns, elimination of seizures and being able to drive and to work. Reduction or elimination of medications and their side effects, however, also are concerns raised by a significant proportion of individuals with epilepsy in general (5–7) and specifically by those considering surgery (8,9).

The pharmacologic management of epilepsy is the subject of a vast literature. Countless studies, reviews, and syntheses document the efficacy of various drugs and discuss which drugs to use for which seizure types or epilepsy syndromes [see sections throughout Engel and Pedley's compendium (10) and the update of Roger et al. of *Le Guide Bleu* (11)]. Discussions are found on the relative merits of monotherapy versus polytherapy (12–18). One can find further discussions on when to initiate treatment, including considerations for and against

starting treatment before or at the onset of epilepsy (19,20). Finally, numerous studies (including one very large randomized trial) and reviews consider the subject of stopping medications in patients once they have become seizure free for a sustained period (20–23). Smaller trials have examined rate of AED discontinuation (24) and time seizure free before attempting discontinuation (25). Thus a wealth of information is available to guide treatment and management decisions in patients with well-controlled epilepsy.

The primary goal (and most common outcome) of resective epilepsy surgery is complete seizure freedom. The likelihood of surgical success and predictors of a good outcome have been thoroughly reviewed by McIntosh et al. (26) Given that a large proportion of patients achieve seizure freedom, it seems there should be some consideration of postsurgical pharmacologic management. Currently little is available on which to base rational recommendations. A review of a selection of epilepsy texts found only one that contained a chapter that specifically addressed the issue of pharmacologic management of the surgical patient (27). The authors provided very sensible recommendations based on their impressions and experience. They recommended monotherapy whenever possible and discussed the possibility that some patients will eventually become drug free. In the end, however, they acknowledged that a dearth of literature and evidence in this area exists and that the field greatly needs well-designed prospective studies.

Pharmacologic Therapy before versus after Surgery

Several observational studies have addressed pharmacologic treatment in patients before versus immediately after surgery and changes in medication over time since surgery (28–31). For example, in the Multicenter Study of Epilepsy Surgery (31), before surgery, approximately one quarter of patients were taking one, about half were taking two, and another quarter were taking three or more AEDs. At discharge, *immediately* after surgery, 31% of patients were taking one, 57% taking two, and 12% (down from one quarter) were taking three or more AEDs.

Wieser and Häne (32) charted the AED loads in a large cohort of selected amygdalohippocampectomy patients from before surgery to up to 15 years after surgery. Before surgery, fewer than 40% were taking monotherapy, approximately 35% were taking two AEDs, and the remaining approximately 25% were taking three or more AEDs. At 5 years after surgery, roughly 35% were off all AEDs, another 35% were receiving monotherapy, about 20% were taking two drugs, and only 10% were taking three or more drugs. After surgery, drug use was substantially

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less in patients with lesional epilepsy (45% off all AEDs and another approximately 35% receiving monotherapy only) compared with patients who had hippocampal sclerosis (~25% off all AEDs and ~35% receiving monotherapy). Similarly, Bien et al. (28) reported substantial changes in medication use from before to after surgery, with only one quarter of patients receiving monotherapy before surgery versus 55% after surgery and another 9% off all AEDs.

In a pediatric cohort, Mathern et al. (29) provided the profile of AED use before surgery and up to 10 years later. The specific findings depended on the underlying pathology: before surgery, one quarter to one half of patients were taking three or more AEDs. By 2 years after surgery, 30% to 40% were taking no AEDs, another 30% to 50% were taking only one AED, approximately 20% were taking two AEDs, and 10% or fewer were taking three or more AEDs.

These reports all reflect very similar experiences. Before surgery, drug loads were high and very comparable among these studies. All studies showed substantial reductions in medication use after surgery, with a large proportion of patients eventually stopping all drugs. How these reductions correspond to or affect seizure outcome is unclear.

Relapse after Surgical Success

Although many patients experience significant remissions from seizures, a substantial proportion of them also experience subsequent relapses. This subject has not been widely publicized in the literature, although numerous reports have touched on it.

The most extensive documentation of the remitting and relapsing patterns of seizures after selected amygdalohippocampectomy is provided by Wieser et al. (30) and forms an important part of the basis for the recent International League Against Epilepsy (ILAE) recommendations regarding classification of postsurgical seizure outcomes (33). During the year immediately after surgery, approximately 55% of patients were completely seizure and aura free, the best possible outcome. Over the next few years, relapses occurred in this “best outcome” group, and by 10 years after surgery, only about 35% were still in this top-outcome category. Thus roughly one third of those who initially had the best outcome immediately after surgery relapsed. Note that at 10 years after surgery, approximately 55% of patients were in remission; however, these were not entirely the same 55% who started off in remission immediately after surgery.

Another recent report retrospectively examined the outcomes of 175 patients who were completely seizure free in the year immediately after surgery (34). All patients were followed up a minimum of 3 years (median, 8 years). The risk of relapse was 17%, 28%, and 44% at 3, 5, and 10 years after surgery, respectively. Of the 65 individuals who relapsed, 9 (13%) did so

after having completely stopped all medications, and 33 (51%) had reduced either the dose or the number of AEDs being taken.

Results from the Australian cohort also indicate a non-negligible risk of late recurrence in patients who, immediately after surgery, were seizure free for at least 2 years, roughly half the cohort (35). In this group with an initially good outcome, approximately one fourth relapsed more than 2 years after surgery.

The studies reviewed earlier were either partially or entirely retrospective in nature. Spencer et al. (36) recently began reporting findings of a large, prospective multicenter study. They found that relapses after a 1-year remission occurred in approximately one third of patients. Even after a 2-year remission, relapses occurred in one fourth of patients (37). Almost half of the relapses occurred in association with medication reduction or elimination.

Reduction versus Elimination of Antiepileptic Drugs

It is helpful to distinguish two arguably separate although related questions: (a) Is a reduction in the number of AEDs from before to immediately after surgery a valid and safe policy? and (b) In seizure-free patients, can one reduce and ultimately eliminate AEDs; what are the risks; and which factors influence these risks?

In response to the first question, one randomized clinical trial compared temporal lobectomy patients randomized to monotherapy versus polytherapy after surgery and found no evidence that polytherapy provided better seizure control than did monotherapy in this specific setting (38). Patients who received polytherapy experienced more side effects than did those receiving monotherapy. Further studies may still be needed to address appropriate management policies for other selected groups of patients. Overall, however, as monotherapy is generally preferred whenever feasible for the management of epilepsy (12,15–18), it would seem that this policy would be favored in the postsurgical treatment of resective surgery patients.

Data on the risk attributable to stopping or reducing medications in postsurgical, seizure-free patients are limited. Schmidt et al. (39) reviewed the available literature and found that in the six studies that met certain predetermined criteria for inclusion in their review, the risk of relapse was approximately one third after stopping AEDs. All studies were retrospective. The most recent and one of the largest of these reported that 7% of patients who had no change in their AEDs relapsed, compared with 26% of those who stopped completely and only 14% who reduced the number of drugs being taken (40). Somewhat different results were found by McIntosh et al. (35). In patients who had been seizure free for 2 years and had a controlled

discontinuation of their medications, the relapse rates were essentially the same as for those who continued taking AEDs.

These studies serve to highlight potential problems with the use of observational data when patients are selected for drug reduction or elimination (or any treatment or management policy) based on factors that we have not yet learned to identify and control in analyses (41,42). Because of the potential for confounding and because we know so little about what selection factors are involved in recommending reducing or stopping AEDs after successful surgery, current data regarding the risk of relapse in this setting must be interpreted very cautiously.

Outcome after Relapse

Although some patients relapsed after reducing or eliminating altogether their AEDs, to the extent that Schmidt et al. (39) were able to consider further outcomes, these patients appeared to do well and regained seizure control. This is an area in need of greater investigation; however, the initial impressions are highly comparable to outcomes seen in people with well-controlled, nonsurgical epilepsy who relapsed after stopping AEDs (43).

Future Directions

With increased interest in offering epilepsy surgery as soon as reasonable, not exhaustive, trials of medications have failed (3,4), an increasing need exists to develop rational recommendations for postsurgical drug management. The issues for the postsurgical, seizure-free individual are likely very similar to those for the nonsurgical, seizure-free individuals. The decision to stop medication is always based on balancing risks versus benefits. This requires, of course, an accurate assessment of the risks associated with both courses, continuation versus reducing and ultimately stopping AEDs. The risks of the latter course include the risk of relapse, the consequences of relapse, and the outcome after relapse.

To understand the best approach to reduction and discontinuation of AEDs, well-designed observational studies can help identify patient characteristics associated with stopping medication in current practice so that we can understand the role of selection in identifying eligible patients. Such studies also should examine the risk of relapse after stopping medication as well as identify predictors of relapse. A large-scale, randomized clinical trial may ultimately be required to provide solid evidence on which to base overall and individualized recommendations regarding reduction and elimination of AEDs in seizure-free, postsurgical patients.

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