
Management of Antiepileptic Drugs following Epilepsy Surgery: A Review

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ABSTRACT: The favourable impact of surgery for intractable epilepsy on seizures is well documented. However, few studies have determined what changes in antiepileptic drug (AED) therapy occur following surgery. Alterations in AED blood levels in the immediate postoperative period can result in breakthrough seizures. In long term follow-up, one-third to one-half of seizure-free patients after temporal lobectomy, the most common type of epilepsy surgery, still require AED treatment which usually has been reduced from polytherapy to monotherapy. In our study of 93 patients followed two years after temporal lobectomy, polytherapy decreased from 78% before surgery to 14% postoperatively, while medication was discontinued in 44%. Early reduction from polytherapy to monotherapy can often be carried out in the immediate postoperative period but the most appropriate timing of cessation of AED treatment has yet to be determined. Patients undergoing extratemporal resections and other forms of epilepsy surgery associated with less favourable postoperative seizure control may achieve comparatively less reduction in antiepileptic medication. We generally do not recommend stopping AEDs prior to one year after surgery.

RÉSUMÉ: Prescription de médicaments anti-épileptiques après la chirurgie de l'épilepsie: revue du sujet. L'impact favorable sur les crises de la chirurgie de l'épilepsie réfractaire au traitement est bien documenté. Cependant, peu d'études ont déterminé quels sont les changements dans le traitement médicamenteux après la chirurgie. Des crises peuvent survenir dans la période postopératoire à cause de modifications dans les taux sanguins de médicaments. Chez les patients suivis à long terme, entre le tiers et la moitié des patients qui n'ont pas de crises après une lobectomie temporale, le type le plus fréquent de chirurgie de l'épilepsie, ont encore besoin d'une médication antiépileptique qu'on a généralement réduit d'une polythérapie à une monothérapie. Dans une étude de 93 patients suivis deux ans après une lobectomie temporale, la polythérapie avait diminué de 78% avant la chirurgie à 14% en période postopératoire, alors que la médication avait été cessée chez 44%. Un passage de la polythérapie à la monothérapie peut souvent être effectué dans la période postopératoire immédiate, mais le moment le plus approprié pour cesser le traitement antiépileptique n'a pas encore été déterminé. Chez les patients qui subissent une résection extratemporale ou d'autres formes de chirurgie de l'épilepsie associées à un pronostic moins favorable sur le contrôle des crises, la diminution de la médication antiépileptique est comparativement moindre. Nous recommandons généralement d'attendre un an avant d'arrêter cette médication après la chirurgie.

Can. J. Neurol. Sci. 2000; 27: Suppl. 1 – S106-S110

Many studies of seizure outcome following epilepsy surgery have been done¹ and more recently, the impact on health-related quality of life has been assessed.^{2,3} However, the postoperative management of antiepileptic drug treatment which impacts on both of these outcome measures has largely been ignored in the literature. This article reviews the existing information on both immediate and longterm treatment with antiepileptic drugs (AEDs) following epilepsy surgery, particularly temporal lobectomy, and suggests possible management strategies.

CHANGES IN ANTIEPILEPTIC DRUGS IN THE IMMEDIATE POSTOPERATIVE PERIOD

Seizures which occur in the first postoperative week have little if any impact on prognosis of seizure outcome.^{1,4} However, the psychological effect of such immediate seizures when the

patient's expectations are high, can be serious. There are many reasons why seizures might occur in the few days or weeks after surgery including direct cortical irritation from the operative procedure and the general stress of undergoing surgery. It is not known if reduction of AEDs, which may occur preoperatively during investigation with EEG telemetry to record seizures or, in some patients, immediately after surgery, increases the risk of early postoperative seizures. Our experience suggests that it is not a major contributing factor. On the other hand, the decrease

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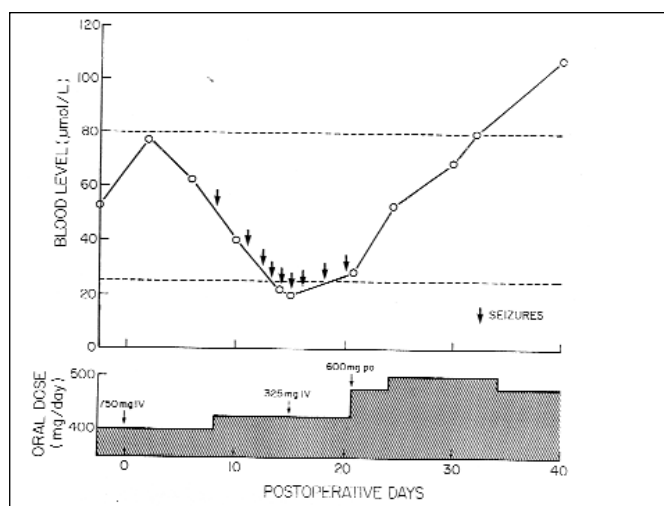


Figure 1: Blood levels and daily dose of phenytoin following temporal lobectomy in a 24-year-old man on phenytoin 400 mg/day preoperatively with blood levels normally 50-60 µmol/L. The therapeutic range is between the dashed lines. Large arrows indicate generalized tonic clonic seizures, a rare occurrence preoperatively. IV=intravenous; po=oral. (From Reference 5).

in AED blood levels, despite stable drug doses which can follow epilepsy surgery (Figure 1) may lead to breakthrough of seizures.⁵ Why this occurs is unknown but several mechanisms have been suggested including accelerated AED metabolism caused by the stress of surgery, changes in bioavailability related to anesthesia or interaction with perioperative drugs such as steroids and antibiotics. Phenytoin and carbamazepine are particularly susceptible to this effect.⁶ If such a change occurs, an increase in the AED dose may be required; however, the blood levels should be followed so that a downward dose adjustment can be made once the postoperative effect has disappeared. Otherwise, the patient could develop drug toxicity once the postoperative destabilizing effect has worn off. Another change in the first postoperative week which has been reported is carbamazepine toxicity caused presumably by a slowed rate of metabolism for the drug as well as its metabolite, carbamazepine-10-11-epoxide.^{7,8} This has not occurred in our experience but we do not routinely measure AED blood levels postoperatively. This is done only if seizures occur or the patient experiences unexpected symptoms.

LONGTERM POSTOPERATIVE MANAGEMENT

Should it be easier to withdraw AEDs in patients who have had epilepsy surgery compared to those who have not? Theoretically, the answer is yes, since in most patients the cortex responsible for ictal discharge has been removed along with any causative pathology. However, no postoperative studies have been done to support this assumption. In medically treated epilepsy, withdrawal of AEDs has been assessed but remains controversial.⁹ After two years remission, AED withdrawal results in seizure recurrence in approximately 30-40% of patients.^{10,11} Although surgery should reduce this rate, this effect could be counteracted by a number of factors in surgically

treated patients which increase the likelihood of recurrence, including syndromes with partial seizures, longstanding intractability before seizure control, polytherapy and in some cases, occurrence of generalized tonic clonic seizures.

Many factors influence the decision to withdraw AEDs including age at surgery, seizure outcome, drug side effects, potential teratogenicity, results of preoperative investigation (i.e. unifocal vs. multifocal abnormalities, temporal vs. extratemporal), whether the patient is driving, employment and individual patient preference. Consideration must also be given to the type of epileptic syndrome being treated and its prognosis.¹² For example, one would be more cautious withdrawing AEDs in patients who have had extratemporal resection and when preoperative investigation showed evidence of multiple foci or a larger epileptic zone than was resected. There is a lack of consensus as to the value of postoperative electroencephalography or electrocorticography in predicting seizure recurrence. Some would argue that the presence of epileptiform transients predicts a poor clinical outcome^{13,14} but others dispute this.^{15,16} Since the aim of the majority of patients is to be off antiepileptic drugs completely, those who are seizure-free will usually want to try stopping medication at some point after surgery.

Polytherapy has been associated with an increased frequency of side effects and poor drug compliance. However, a recent study suggests that total drug dose may be more important than the number of AED's.¹⁷ Despite a number of studies which emphasize monotherapy for the treatment of epilepsy,¹⁸⁻²¹ most patients considered for epilepsy surgery are on polytherapy. In the few studies which report antiepileptic drug outcome after epilepsy surgery, there appears to be a trend over time from polytherapy to monotherapy after surgery. Wieser²² reported on 52 patients with a minimum one year follow-up after amygdalo-hippocampectomy, in whom 52% were still on polytherapy, 27% were on monotherapy and 21% on no antiepileptic drugs. Similarly, data from one of our centres on 72 patients following temporal lobectomy found that polytherapy decreased from 80% of patients preoperatively to 20% two years postoperatively.² In a series of 124 adults, with mean follow-up of 16 years after epilepsy surgery for partial epilepsy including both temporal and extratemporal resections, 51% remained on polytherapy compared to 23% on monotherapy and 26% who had discontinued medication.²³ More recently, Vickrey et al³ found after a mean follow-up of 5.8 years that the mean number of AEDs used per patient fell from 2.28 preoperatively to 1.36 postoperatively following temporal or extratemporal resection. Interestingly, in the two controlled studies of epilepsy surgery, there is a less striking but definite decrease in the use of antiepileptic drugs by patients with intractable epilepsy who did not have surgery and were followed for the same length of time.^{2,3} One study of children undergoing temporal or extratemporal resections has found that at a mean follow-up of 2.7 years, 30% had discontinued antiepileptic drugs while another 30% were on "reduced medication".²⁴

We have carried out a retrospective study of 93 patients who had temporal lobectomy and were followed at 6, 12, and 24 months after surgery.²⁵ Figure 2 shows the percent of patients on polytherapy, monotherapy or no AED treatment at the four time intervals. There was a striking reduction in patients on

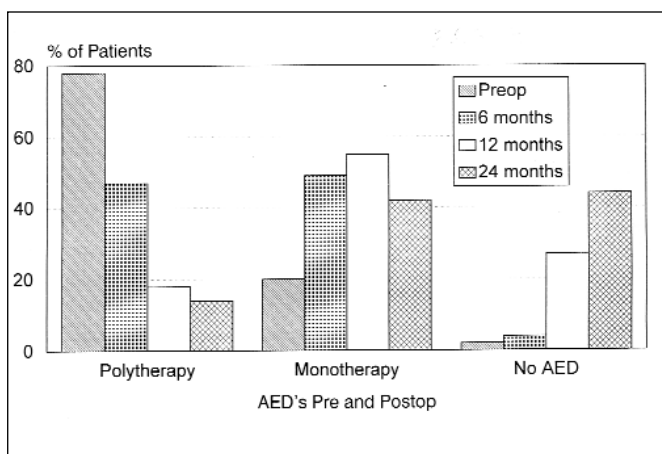


Figure 2: Number of AEDs used preoperatively and at 6, 12 and 24 months in 93 patients after temporal lobectomy showing reduced polytherapy over time but an increase in monotherapy and no drug use.

polytherapy from 78% before surgery to only 14% at two years follow-up. Treatment with monotherapy went from 20% to 42% and medication was discontinued in 44% of patients. The most commonly used drugs, both before and after surgery, were carbamazepine, phenytoin and clobazam (Figure 3). The number of patients using both carbamazepine and clobazam dropped considerably following surgery but interestingly, there was little change in the group using phenytoin. This may reflect a concern in these patients about recurrence of generalized tonic clonic seizures. Although the number of AEDs used decreased significantly after surgery, there was no difference in the daily doses of the remaining drugs (Figure 4).

As expected, the postoperative AED use reflected degree of seizure control with 53% of seizure-free patients having discontinued AEDs compared to only 33% who continued to have at least some seizures. This is similar to unpublished data from the University of Washington discussed by Andermann et al.¹² Four to five years after temporal resection, 67% of their seizure-free patients were on no AEDs compared to 50% with five or fewer seizures per year and 7% with more than five seizures per year. Thus, about a third to a half of patients still appear to require AEDs to remain seizure-free after surgery, most with monotherapy. That a third of patients who remain uncontrolled elect not to take medications is not surprising, since many of these patients have a considerable decrease in severity, as well as frequency of postoperative seizures.

TIMING OF POSTOPERATIVE ANTIEPILEPTIC DRUG CHANGES

Reduction and eventual withdrawal of AED treatment is one of the aims of epilepsy surgery but there are limited data to help determine when these changes should occur. Andermann et al suggest that no changes be made for "an arbitrary period of one year" and that cessation of AEDs be considered after two to three years.¹² This is in line with withdrawal of medication following seizure control with medical management.^{10,11} Kuzniecky et al specifically addressed the timing of change in AED treatment following surgery in an open label, randomized trial of

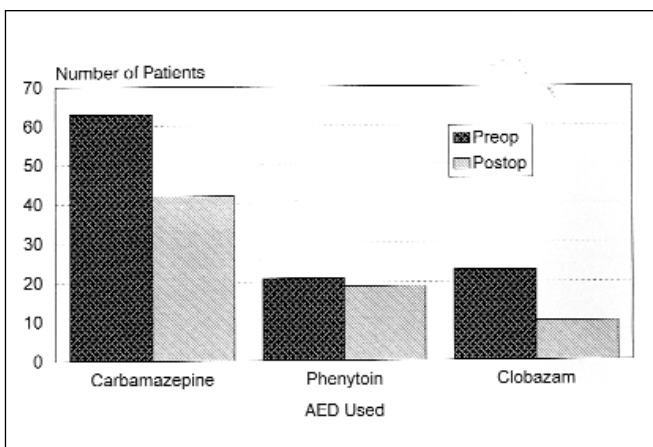


Figure 3: Use of individual AEDs preoperatively compared to 24 months postoperatively (n=93). There is a decrease in the number of patients taking carbamazepine and clobazam but not phenytoin.

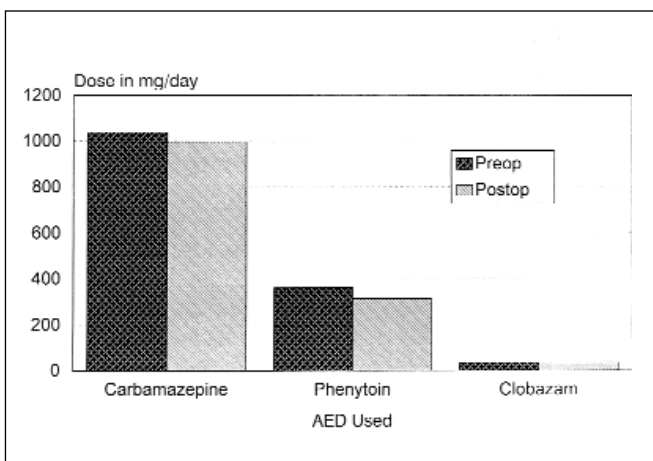


Figure 4: Daily doses of AEDs preoperatively compared to 24 months postoperatively (n=93) show no substantial changes.

postoperative carbamazepine monotherapy versus polytherapy in 40 patients undergoing temporal lobectomy.²⁶ Half the patients continued with presurgical polytherapy and half were changed to monotherapy at the time of surgery. Outcome determined at one year follow-up found that seizure recurrence was no different in the two groups but those on polytherapy had three times the incidence of drug-related side effects. The prevalence of side effects in this study is consistent with what has previously been reported with general medical management.²⁷ Our data support their findings, since most of our patients were reduced from polytherapy to monotherapy within six months of surgery with no apparent impact on seizures.

Although early reduction in the amount of medication appears to be a reasonable approach, it is less clear when AEDs should be discontinued. Our study found that cessation of therapy one to two years after temporal lobectomy was not associated with untoward effects on seizures but this was a qualitative not quantitative assessment. However, the argument

can be made that if a patient is seizure-free on a single AED such as carbamazepine, without side effects, why “rock the boat”? In other words, why risk having a seizure when someone is doing well. Unfortunately, there are no data to allow physicians to present the risk of seizure recurrence if AEDs are stopped following surgery. This is one explanation why 47% of our seizure-free patients were still on medication two years after surgery. We do not recommend stopping AEDs prior to one year follow-up but after that, patients should be allowed to determine when they feel comfortable with discontinuing medication under the guidance of their neurologist.

POTENTIAL IMPACT OF AED WITHDRAWAL

The decrease from polytherapy to monotherapy which commonly occurs following epilepsy surgery is associated with a reduction in drug-related side effects²⁶ and in our experience, is seldom associated with seizures in otherwise controlled individuals. If a seizure does occur, it is usually when AEDs have been withdrawn completely. For some patients, the recurrence of seizures after surgery can be psychologically distressing; thus patients must be prepared for the possibility of seizure recurrence including the chance of a generalized tonic clonic seizure. They should be told that in the event of a seizure, medication will be re-introduced usually with return to a seizure-free state. There may be rare instances in which seizure control cannot be re-established but this is not well documented. Another rare occurrence is the development of the first episode of status epilepticus in the months following surgery, possibly in part related to reduced medication. Finally, the new onset of pseudoseizures has been documented after surgery²⁸ and these, of course, do not respond to changes in AED therapy.

RECOMMENDATIONS

Since there are few data from clinical studies of postoperative antiepileptic drug reduction, the following recommendations are based largely on empirical evidence from experience at our centres and apply mainly to patients undergoing temporal lobectomy. More specific guidelines hopefully will evolve from prospective trials of AED withdrawal after epilepsy surgery.

- 1) An early goal of resective epilepsy surgery is the reduction of polytherapy to monotherapy. If AEDs have been reduced during preoperative AED telemetry, we often leave the patient on the lower amount of medication if surgery is going to be carried out within a few days or weeks. This usually implies going from three to two or from two to one AEDs.
- 2) If monotherapy has been used preoperatively, either no change is made or in some cases, a slight lowering of dose can be initiated five or six days after surgery and prior to discharge from hospital.
- 3) If monotherapy has not been achieved at the time of discharge, a gradual reduction in medication can be started six months postoperatively until this goal is reached or a seizure occurs.
- 4) Patients on monotherapy who are seizure-free for one or preferably two years can be offered the opportunity to withdraw medication utilizing published guidelines for drug withdrawal following medical management.^{29,30}
- 5) For extratemporal resections and particularly other

procedures such as corpus callosotomy, a more cautious approach in reducing AEDs is required since complete seizure control is less likely to be achieved than following temporal lobectomy. An exception to this is hemispherectomy for which postoperative monotherapy can often be used prior to complete drug withdrawal.

REFERENCES

1. Engel J, Van Ness PC, Rasmussen TB, Ojemann LM. Outcome with respect to epileptic seizures. In: Engel J, ed. *Surgical Treatment of the Epilepsies*. 2nd ed. New York: Raven Press, 1993; 609-621.
2. McLachlan RS, Rose K, Derry PA, et al. Health-related quality of life and seizure control in TLE: a prospective comparison of surgical and medical management. *Ann Neurol* 1997; 41:482-489.
3. Vickrey BG, et al. Outcomes in 248 patients who had diagnostic evaluations for epilepsy surgery. *Lancet* 1995; 346:1445-1449.
4. Wingkun ED, Awad IA, Luders H, Awad CA. Natural history of recurrent seizures after resective surgery for epilepsy. *Epilepsia* 1991; 32:851-856.
5. McLachlan RS. Medical management of epilepsy and theoretical basis for surgical therapy. In: Varkey GP, ed. *Anesthetic Considerations for Craniotomy in Awake Patients*. Boston: Little Brown, 1986:31-45.
6. Ojemann GA, Bourgeois BF. Early postoperative management. In: Engel J, ed. *Surgical Treatment of the Epilepsies*. 2nd ed. New York: Raven Press, 1993:539-540.
7. Cruz-Rodriguez RF, Graves NM, Leppik IE, Wilder R. Carbamazepine toxicity after epilepsy surgery. *Epilepsia* 1989; 30:640.
8. Gidal BE, Spencer NW, Maly MM, Pitterle ME. Evaluation of carbamazepine and carbamazepine-epoxide protein binding in patients undergoing epilepsy surgery. *Epilepsia* 1996; 37:381-385.
9. Duncan JS, Shorvon SD, Fish DR. *Clinical Epilepsy*. New York: Churchill Livingstone, 1995:224-228.
10. Chadwick D, Reynolds EH. When do epileptic patients need treatment? Starting and stopping medications. *Br Med J* 1985; 290:1885-1888.
11. Callaghan N, Garrett A, Goggin T. Withdrawal of anticonvulsant drugs in patients free of seizures for two years. *N Engl J Med* 1988; 318:942-946.
12. Andermann F, Bourgeois BF, Leppik IE, Ojemann LM, Sherwin AL. Postoperative pharmacotherapy and discontinuation of antiepileptic drugs. In: Engel J, ed. *Surgical Treatment of the Epilepsies*. 2nd ed. New York: Raven Press, 1993:679-684.
13. Tuunainen A, Nousiainen U, Mervaala E, et al. Postoperative EEG and electrocorticography: relation to clinical outcome in patients with temporal lobe surgery. *Epilepsia* 1994; 35:1165-1173.
14. Godoy J, Lüders H, Dinner DS, et al. Significance of sharp waves in routine EEGs after epilepsy surgery. *Epilepsia* 1992; 33:285-288.
15. So N, Olivier A, Andermann F, Gloor P, Quesney LF. Results of surgical treatment in patients with bitemporal epileptiform abnormalities. *Ann Neurol* 1989; 25:432-439.
16. Kanazawa O, Blume WT, Girvin JP. Significance of spikes at temporal lobe electroencephalography. *Epilepsia* 1996; 37:50-55.
17. Deckers CLP, Hekster YA, Keyser A, Meinardi H, Renier WO. Reappraisal of polytherapy in epilepsy: a critical review of drug load and adverse effects. *Epilepsia* 1997; 38:570-575.
18. Reynolds EH, Shorvon SD. Monotherapy or polytherapy for epilepsy. *Epilepsia* 1981; 22:1-10.
19. Albright P, Bruni J. Reduction of polytherapy in epileptic patients. *Arch Neurol* 1982; 23:531-544.
20. Schmidt D. Reduction of two-drug therapy in intractable epilepsy. *Epilepsia* 1983; 24:368-376.
21. Thompson PJ, Trimble MR. Anticonvulsant drugs and cognitive functions. *Epilepsia* 1982; 23:531-544.
22. Wieser HG. Selective amygdalohippocampectomy for temporal

- lobe epilepsy. *Epilepsia* 1988; 29:S100-S113.
23. Guldvog B, Loyning Y, Hauglie-Hanssen E, Flood S, Bjornaes H. Surgical treatment for partial epilepsy among Norwegian adults. *Epilepsia* 1994; 35:540-553.
 24. Gilliam F, et al. Epilepsy surgery outcome: comprehensive assessment in children. *Neurology* 1997; 48:1368-1374.
 25. Maher J, McLachlan RS. Antiepileptic drug treatment following temporal lobectomy. *Neurology* 1998; 51:305-307.
 26. Kuzniecky R, Rubin ZK, Faught E, Morawetz R. Antiepileptic drug treatment after temporal lobe epilepsy surgery: a randomized study comparing carbamazepine and polytherapy. *Epilepsia* 1992; 33:908-912.
 27. Schmidt D. Adverse effects. In: Frey H, Janz D, eds. *Antiepileptic Drugs: Handbook of Experimental Pharmacology*. Berlin: Springer-Verlag, 1985:791-829.
 28. Krahn Le, Rummans TA, Sharbrough FW, Jowsey SG, Cascino GD. Pseudoseizures after epilepsy surgery. *Psychosomatics* 1995; 36:487-493.
 29. Greenberg MK, et al. Practice parameter: a guideline for discontinuing antiepileptic drugs in seizure-free patients-summary statement. *Neurology* 1996; 47:600-602.
 30. Schmidt D, Gram L. A practical guide to when (and how) to withdraw antiepileptic drugs in seizure-free patients. *Drugs* 1996; 52:870-874.