Withdrawal of Antiepileptic Drugs Following Surgical Treatment of Drug-Resistant Epilepsy

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Abstract

The number of patients with successful outcomes following surgical treatment of drug-resistant epilepsy has been rapidly increasing. This trend has heightened the relevance of addressing the appropriateness of postoperative withdrawal of antiepileptic drugs (AED). There are no unified guidelines regarding the optimal timing and rates for discontinuing pharmacological therapy. This article reviews the timing, rate, and specifics of AED withdrawal following surgical treatment of drug-resistant epilepsy using two exemplary clinical cases. The decision to discontinue pharmacotherapy depends on multiple factors, including patient preferences. In cases of favorable outcomes following epilepsy surgery, AED withdrawal one year into remission is considered safe and does not affect long-term seizure outcomes in adult patients who have undergone anterior temporal lobectomy, remain completely seizure- and aura-free, and show no epileptiform activity on electroencephalography. Patients with multiple epileptogenic zones, epileptiform EEG activity, or persistent seizures/auras have less favorable prognoses regarding AED withdrawal.

Keywords: *epileptic seizures; structural epilepsy; drug resistance; epilepsy pharmacotherapy; antiepileptic drug withdrawal; epilepsy surgery*

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Отмена противоэпилептических препаратов после хирургического лечения фармакорезистентной эпилепсии

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Аннотация

Количество пациентов с успешным исходом после хирургического лечения фармакорезистентной эпилепсии стремительно увеличивается. На этом фоне возрастает актуальность вопроса о целесообразности послеоперационной отмены противоэпилептических препаратов (ПЭП). Единые рекомендации относительно оптимальных сроков и скорости отмены лекарственной терапии отсутствуют. В статье проанализированы сроки, скорость и особенности отмены ПЭП после хирургического лечения фармакорезистентной эпилепсии на примере двух клинических случаев. Решение об отмене фармакотерапии складывается из множества факторов, в том числе с учётом настроя пациента. В случае благоприятного исхода после хирургического лечения эпилепсии отмена ПЭП после 1 года ремиссии считается безопасной и не влияет на долгосрочный исход приступов у взрослых пациентов после передневисочной лобэктомии, полностью свободных от приступов и их предчувствий, не имеющих эпилептиформной активности на электроэнцефалограмме. Менее благоприятный прогноз при отмене ПЭП имеют пациенты с несколькими эпилептогенными зонами, эпилептиформной активностью на электроэнцефалограмме, с сохраняющимися приступами или аурами.

Ключевые слова: *эпилептические приступы; структурная эпилепсия; фармакорезистентность; фармакотерапия эпилепсии; отмена противоэпилептических препаратов; хирургия эпилепсии*

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Introduction

Surgical treatment of epilepsy allows many patients to achieve complete seizure freedom [1]. Remission of epileptic seizures is the goal of surgical intervention for drug-resistant epilepsy. However, patients typically consider themselves healthy only after complete withdrawal of antiepileptic drugs (AEDs) [2].

The data on AED use following successful epilepsy surgery are limited. Clinical guidelines for managing patients and discontinuing pharmacotherapy after epilepsy surgery are lacking. The issue of postoperative drug therapy is relevant both for patients and neurologists due to reduced quality of life, cognitive impairment, and/or adverse drug reactions in patients [3]. Therefore, understanding patient motivation and potential concerns regarding AED withdrawal is crucial [4]. Practices for AED discontinuation vary across centers and countries. Physicians have significant disagreements regarding management strategies and timing of medication withdrawal after surgical treatment [5].

Some studies have shown that AEDs can be successfully discontinued in 30–50% of patients after anterior temporal lobectomy [6, 7]. However, the optimal timing for initiating withdrawal and long-term outcomes in patients undergoing pharmacotherapy discontinuation remain undefined. The likelihood of seizure recurrence with early AED withdrawal compared to late discontinuation or continued therapy has not been sufficiently studied [8].

We present care reports of patients who achieved seizure freedom following surgical treatment and discontinued AEDs.

Case report 1

Patient S., 40 years old. Epilepsy began at the age of 14 with focal motor seizures accompanied by oropharyngeal automatisms and automatism-related seizures. Magnetic resonance imaging (MRI) revealed right hippocampal sclerosis. Video-EEG monitoring demonstrated interictal regional epileptiform activity in the right temporal region. The patient's history included an episode of febrile seizures at the age of 3.

Over several years, continuous modification of antiseizure treatment was made using both monotherapy and various combination regimens, yet epileptic seizures persisted. During AED therapy, the patient experienced adverse reactions including diffuse alopecia, thrombocytopenia, menstrual cycle irregularities, and Landolt's syndrome. Despite therapeutic adjustments, the frequency of epileptic seizures progressively increased. In 2013, due to pharmacoresistant disease, a neurosurgical consultation was conducted to evaluate potential surgical intervention. In 2014, a right temporal lobectomy was performed. The postoperative course was uneventful. Histological examination of resected tissue revealed morphological pattern consistent with hippocampal sclerosis.

At the time of surgery, the patient was receiving AED polytherapy with valproic acid, oxcarbazepine, and lacosamide at moderate therapeutic doses. Two and a half months postoperatively, a single focal motor seizure was observed. EEG revealed periodic slowing of cortical rhythms in the right frontotemporal region near the surgical site. One and a half years postoperatively during the first trimester of pregnancy, the patient self-discontinued lacosamide due to medication access challenges, which coincided with a single nocturnal bilateral tonic-clonic seizure. No further epileptic seizures occurred thereafter. Two and a half years after epilepsy surgery, a decision was made for gradual sequential AED withdrawal. The patient has now maintained complete clinical and electroencephalographic remission of epileptic seizures for 10 years.

Case report 2

Patient K., 35 years old. Epilepsy began at the age of 16, presenting with focal non-motor (cognitive, sensory) and motor seizures accompanied by oroalimentary and hand automatisms, occurring with both preserved and impaired

consciousness, and periodic evolution into bilateral tonic seizures. Over several years, the most effective AED combination was gradually selected, with epileptic seizures of varying frequency documented. Neuroimaging revealed an encephalocele in the basal surface of the left temporal lobe. EEG findings showed focal epileptiform activity in the left temporal region.

In 2017, the patient underwent microsurgical resection of the epileptogenic focus in the left temporal lobe and left temporal pole resection under neurophysiological monitoring. At the time of surgery, the patient was on dual therapy with two medications: valproic acid and oxcarbazepine at adequate daily doses. On the first day postoperatively, two seizures with impaired awareness were recorded. Over the next six months, the patient reported sporadic brief déjà vu episodes. Subsequently, epileptic seizures were absent, and EEG demonstrated regional cortical slowing in the left temporal lobe at the encephalocele resection site, with no epileptiform activity registered. Consequently, gradual dose reduction of valproic acid and oxcarbazepine was recommended 2.5 years after surgery. To date, both clinical and electroencephalographic remission of epileptic seizures has been maintained for over seven years.

Discussion

In 2017, the International League Against Epilepsy introduced the concept of "resolution of epilepsy" [9]. Epilepsy is considered resolved in patients with age-dependent epileptic syndromes who have reached a specific age, or in patients who have been free of epileptic seizures for 10 years, including those who have been off AEDs for the last 5 years. There are no specific guidelines for declaring epilepsy resolution in patients following surgery, although surgical treatment is considered the only potential cure for the disease [2]. Additionally, there is no clear definition of «remission of epilepsy,» which creates challenges for both patients and practicing neurologists[1].

According to M.T. Foged et al., complete cure following resective epilepsy surgery is defined by the absence of both seizures and AED use [10]. Significant reduction observed both in the number and daily maintenance dosages of AED following each year of treatment may be an indirect measure of the effectiveness of epilepsy surgery. [11].

There are no unified guidelines to assist in deciding the timing of AED withdrawal or management strategies for patients after successful epilepsy surgery. Various neurosurgical centers employ different approaches to discontinuing AEDs postoperatively [8]. Most commonly, pharmacotherapy continues for at least 2 years following epilepsy surgery due to the potential risk of seizure recurrence and the possibility of failing to achieve remission even after AED resumption [12].

So, M.T. Foged et al. demonstrated that 62% of patients who achieved 3-year seizure remission after successful epilepsy surgery still continued AED therapy. Of those, 20% maintained the same AED dose, while 50% were unwilling to adjust treatment voluntarily. Seven years post-surgery, 18% of patients continued AED use despite sustained seizure remission [10].

Approaches to determining the rate of AED withdrawal require individualized decision-making. Specifically, there is insufficient evidence regarding whether and when to discontinue AEDs, the patient profile suitable for medication withdrawal, or the relapse risks associated with discontinuation [10, 13].

According to C. Rathore et al., many centers discontinue AEDs early in the postoperative period following epilepsy surgery, while others extend pharmacotherapy indefinitely [8].

Some studies report that patients with early gradual AED dose reduction achieved complete seizure remission at rates comparable to those continuing AED therapy [2, 14, 15]. Conversely, an earlier study by D. Ladino et al. found that 1 in 5 surgically treated patients experienced seizure recurrence after medication withdrawal [6].

Several studies indicate that the average time to initiate AED withdrawal ranged from 1.0 to 3.6 years post-surgery, with relapses occurring in only 15% of patients who discontinued therapy [14, 16].

A 1-year seizure-free period following anterior temporal lobectomy is generally considered the minimum standard before attempting AED withdrawal, as over 80% of recurrences occur within the first postoperative year. A single seizure during the first postoperative year increases the likelihood of subsequent seizures sixfold [7, 17]. C. Rathore et al. demonstrated that early complete AED withdrawal starting 1 year after anterior temporal lobectomy is associated with a higher risk of early seizure recurrence compared to continued AED therapy. However, delaying withdrawal until 3 years post-surgery does not protect against potential recurrences, with similar relapse rates and long-term outcomes observed between early and delayed withdrawal groups. Thus, early AED withdrawal starting 1 year after anterior temporal lobectomy appears safe and does not affect long-term seizure outcomes in adult patients [8].

Nevertheless, many clinicians hesitate to discontinue AEDs due to one or more factors: occurrence of seizures in the early postoperative period, epileptiform activity on EEG, age at epilepsy onset and seizure characteristics, and fear of relapse.

In the first clinical case presented, the patient experienced a single focal motor seizure 2.5 months after surgical treatment for drug-resistant epilepsy, and a single nocturnal bilateral tonic-clonic seizure 1.5 years postoperatively during pregnancy and following self-discontinuation of one of AEDs. Subsequently, no epileptic seizures were observed, with an Engel Class Ic outcome. Gradual discontinuation of the second AED was recommended 2.5 years after surgery.

In the second case, two seizures with fluctuating consciousness levels were recorded in the first 24 hours postopera-

[1]Ayvazyan SO, Akzhigitov RG, Alferova VV, et al. Epilepsy and status epilepticus in adults and children. Clinical recommendations, 2022. URL: https://cr.minzdrav.gov.ru/recomend/741_1 (Accessed: February 14, 2025).

tively, followed by isolated brief aura episodes over the next six months, resulting in an Engel Class Ib outcome. This necessitated prolonged AED use, with gradual discontinuation initiated only 2.5 years postoperatively.

Multiple studies indicate that preoperative and postoperative generalized tonic-clonic seizures influenced the decision to continue therapy in approximately half of cases. Post-discharge seizure recurrence, persistent auras, and postoperative epileptiform EEG abnormalities were generally decisive factors against AED discontinuation [18, 19].

In our cases, both patients exhibited regional slowing in the resected epileptogenic zone. Similar patterns may occur in patients with structural brain damage. Additionally, postoperative patients may demonstrate breach rhythm – an artifact associated with skull defects [20]. This artifact superimposed on slow waves can mimic epileptiform activity and, if misinterpreted, may influence clinical decision-making regarding patient management [21].

In the survey by A.T. Berg et al., 9 out of 10 respondents considered epileptiform EEG activity a critical concern against AED withdrawal [18]. A quarter of respondents viewed it as the sole or predominant factor. Conversely, focal slowing and nonspecific findings had no impact on approximately 80% of respondents.

Neuroimaging in our first case revealed right hippocampal sclerosis, while the second case showed encephalocele at the basal surface of the left temporal lobe, both histologically confirmed. Both cases shared well-defined focal pathology concordant with the epileptogenic zone and resection area, likely contributing to favorable surgical outcomes and eventual AED withdrawal despite postoperative seizures.

In A.T. Berg et al. study, MRI-detected unilateral medial hippocampal sclerosis favored AED discontinuation for nearly 75% of respondents, whereas multifocal or bilateral MRI findings were contraindications [18]. Physician responses regarding other brain pathologies varied significantly, though nearly 90% agreed that malignant tumors contraindicated AED discontinuation.

According to a number of authors, maintenance of seizure remission after AED withdrawal can be expected in carefully selected patients. Most commonly, these are patients with mesial temporal sclerosis and a history of febrile seizures [7, 22]. Notably, in the first clinical case described, the patient had a single documented episode of febrile seizures at 3 years of age.

The absence of febrile seizures in the medical history is associated with a higher risk of relapse after epilepsy surgery following AED discontinuation. J. Janszky et al. report that a history of febrile seizures and relatively late age of epilepsy onset are useful diagnostic indicators for clinicians [23]. These patients demonstrate better outcomes following temporal lobectomy compared to those with hippocampal sclerosis but no history of febrile seizures.

Women of childbearing age often express concerns about potential AED teratogenicity, which may motivate attempts to reduce medication doses, ideally long before actual pregnancy planning [24]. In our case, self-discontinuation of one of three AEDs coincided with pregnancy onset, followed by a single seizure occurring 1.5 years post-surgery. Approximately 19–50% of pregnant women with epilepsy do not adhere to prescribed AED therapy, with seizure exacerbation during gestation observed in 90% of these cases compared to 9.8% in treatment-compliant women [25, 26].

Furthermore, a correlation has been demonstrated between seizure frequency during pregnancy and sex steroid hormone levels [27]. Seizure frequency increased with elevated estrogen and reduced progesterone levels, attributable to the pro-epileptogenic effects of estradiol. A similar hormonal effect was observed in the first clinical case.

Other reasons for AED discontinuation may include treatment costs and patients' desire to perceive themselves as «cured» while avoiding the inconvenience and stigma of daily medication use [4]. Up to 88% of patients experience AED-related adverse effects, including dizziness, lethargy, cognitive impairment, and neuropsychiatric symptoms that may negatively impact quality of life [28, 29].

The concepts of early and late seizure relapses following epilepsy surgery remain undefined in clinical guidelines. A.M. McIntosh et al. defined late seizure recurrence was defined as a first postoperative seizure > 2 years after surgery [30]. In cases of late recurrence following AED withdrawal, 71% of respondents reported typically resuming their last used AED, 13% initiated a different AED, and 16% did not resume pharmacological treatment. When seizures recur, most patients regain seizure control after treatment re-initiation, though up to 20% fail to achieve immediate remission [14]. Some authors report that patients experiencing seizure relapse due to AED dose reduction are more likely to regain epilepsy control than those with relapses from other causes [31].

According to K.I. Park et al., post-AED withdrawal seizure relapse can be readily controlled in most patients; however, therapy discontinuation carries a risk of future development of drug-resistant epilepsy [32]. Some patients may not maintain seizure freedom achieved during the first several postoperative years. Several studies have reported late seizure relapses, though these remain underinvestigated due to limited availability of large cohorts with extended follow-up periods [33, 34].

Additional risk factors for postoperative seizure relapse following AED withdrawal include: age >30 years at surgery, long disease duration, residual gliotic changes on postoperative MRI, focal cortical dysplasia as epilepsy etiology, and neurological deficits [19].

Conclusion

The decision to continue or discontinue AED treatment requires an individualized assessment of risks and benefits for the patient. One of the primary concerns is the recurrence of epileptic seizures following treatment discontinuation. It is crucial to engage patients in discussing whether this risk outweighs the potential benefits of AED withdrawal. Patients'

concerns and motivations for discontinuing AEDs must be thoroughly explored. The decision should be personalized, incorporating clinical and electroencephalographic data.

Thus, discontinuing AED therapy requires consideration of numerous factors. Further large-scale studies are needed to establish management strategies for patients after successful epilepsy surgery, including identifying the optimal timing for initiating AED withdrawal. Additionally, identifying early predictors of outcomes in surgical treatment for drug-resistant epilepsy remains an important objective.

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