RESEARCH ARTICLE

Timing for Starting Antiseizure Medication Withdrawal After Epilepsy Surgery in Adults

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Abstract

Background and Objectives

More than half of people undergoing epilepsy surgery become seizure-free and may consider withdrawing antiseizure medications (ASMs). Withdrawal practices vary, and the optimal timing remains unclear. We aim to compare seizure relapse risk among individuals initiating ASM withdrawal at different time points after epilepsy surgery.

Methods

We conducted a multicenter observational cohort study of adults who underwent resective epilepsy surgery between 1990 and 2016 at 12 tertiary centers. Participants were seizure-free before medication withdrawal and had at least 1 year of follow-up. Seizure relapse risk was compared among those initiating withdrawal 1, 2, 3, 4, or 5 years postoperatively vs later. We used propensity score matching for each comparison to adjust for treatment selection bias.

Results

Of the 964 people included (51% female; median age at surgery 34 years [interquartile range 26–44]), 446 (46%) began ASM withdrawal in the first year after surgery, 255 (26%) in the second, 110 (11%) in the third, 58 (6%) in the fourth, 29 (3%) in the fifth, and 66 (7%) after the fifth year. After matching, those starting withdrawal in the first (hazard ratio [HR] 1.4; p = 0.003) or second (HR 1.18; $p < 0.001$) year had a higher risk of relapse than those who withdrew later. Starting withdrawal in the third (HR 1.7; $p = 0.12$), fourth (HR 1.3; $p = 0.45$), or fifth (HR 0.17; p = 0.82) year after surgery showed no increase in risk compared with later withdrawal. Long-term outcomes, such as seizure freedom and being entirely off ASMs at the final follow-up, were not substantially associated with withdrawal timing.

Discussion

Initiating ASM withdrawal within the first 2 postoperative years was linked to a higher initial risk of seizure relapse compared with later withdrawal, although long-term outcomes were similar regardless of withdrawal timing. Waiting more than 2 years did not confer additional benefit in reducing seizure risk. Deciding whether and when to withdraw ASMs is a shared process involving individuals, caregivers, and clinicians, balancing preferences, risk of injury, social factors (e.g., driving, work, and supervision), and clinical judgment. Transparent information on risks and benefits is essential. Our findings offer real-world evidence that may inform future evidence-based withdrawal protocols and follow-up strategies.

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Supplementary Material

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Glossary

ASM = antiseizure medication; **HR** = hazard ratio; **ILAE** = International League Against Epilepsy; **IQR** = interquartile range; **IRB** = institutional review board; **PSM** = propensity score matching; **SMD** = standardized mean difference.

Introduction

More than half of adults undergoing resective epilepsy surgery achieve seizure freedom[1,2] and may consider antiseizure medication (ASM) withdrawal.[3] Continued ASM treatment may have adverse effects that reduce quality of life, increase health care costs, and pose teratogenic risks.[4,5] Conversely, withdrawing ASMs may result in seizure relapse, which can cause injuries, stigma, and restrictions on activities such as driving.[6]

Estimating relapse risks is crucial to identifying individuals who would benefit from ASM withdrawal and establishing optimal discontinuation protocols.

We previously identified the factors associated with seizure relapse after ASM withdrawal following epilepsy surgery and developed prognostic models[7] incorporating variables significantly linked to relapse risk.[3] Independent predictors of seizure recurrence included focal preserved consciousness seizures after surgery and before withdrawal, history of generalized tonic-clonic seizures before surgery, shorter time from surgery to the start of ASM withdrawal, and a higher number of ASMs at the time of surgery. Although time to begin withdrawal was identified as a significant variable, there is currently no evidence to define the ideal timing for ASM discontinuation.

In practice, the decision on when to withdraw ASMs is influenced by clinicians' risk assessments, local standards, and individual preferences, leading to wide variability in withdrawal strategies.[6,8-12] Early withdrawal has been associated with an elevated risk of relapse,[3,6,13] but robust evidence on the ideal timing is lacking. In nonsurgical settings, ASM reduction typically occurs after at least 2 years of seizure freedom,[6,8,9,12-15] a practice often extrapolated to postsurgical care.[16] Some studies have reported that early withdrawal (<2 years) increases relapse risk,[17-21] whereas others suggest no impact on long-term outcomes and note that early withdrawal may help unmask surgical failures.[16,19,22] The effect of timing seems to become clinically insignificant beyond a specific interval.[16] Determining this threshold time would greatly aid in clinical decision making and inform evidence-based management guidelines.

Given the heterogeneous and inadequate evidence surrounding early vs late ASM withdrawal, we evaluated the impact of withdrawal timing on seizure outcomes after epilepsy surgery in adults. Specifically, we assessed whether initiating ASM withdrawal within a defined time frame affects seizure relapse risk or long-term outcomes compared with waiting longer. We sought to identify the point after which waiting longer confers no additional benefit.

Methods

Study Population

We analyzed data from a multicenter registry of ASM withdrawal after epilepsy surgery in adults, encompassing 12 international cohorts (eMethods 1). Nine cohorts have been previously reported.[3] Three new cohorts were added: Brno, Czechia; Shiraz, Iran; and Zurich, Switzerland.

We included consecutive adults who underwent resective epilepsy surgery, had at least 1 year of postoperative follow-up after surgery, and were seizure-free (i.e., International League Against Epilepsy [ILAE] outcome class 1) before beginning ASM withdrawal and initiated ASM reduction. We only included those who started ASM tapering with the goal of withdrawal, which was determined by revision of clinical notes.

We excluded people who were not seizure-free before starting ASM reduction (ILAE outcome class ≥2), did not attempt withdrawal, underwent disconnective procedures, had multiple brain surgeries, or had less than 1 year of follow-up after surgery. Postoperative seizures within 30 days of resective surgery were not considered relapses.[23] Postsurgical seizure outcomes were determined annually using the ILAE outcome scale, and medication regimens were documented. The study flowchart and description of how patients were identified and how outcomes were verified are presented in eFigure 1.

Outcomes

The primary outcome was time to any seizure relapse after the start of ASM withdrawal, with observations censored at relapse or last follow-up. For long-term outcomes, we evaluated seizure freedom, medication status (completely withdrawn from ASMs), and "ASM-free remission" (which we defined as seizure-free and not taking ASMs) during the final year of follow-up.

Statistical Analysis

We compared outcomes among individuals who began ASM withdrawal during specific postoperative time frames (e.g., first year vs later and second year vs later). We conducted 5 separate analyses: first postoperative year vs later, second year vs later, third year vs later, fourth year vs later, and fifth year vs later.

The timing of ASM withdrawal is subject to treatment selection bias, because those with perceived higher relapse risk or greater severity may delay withdrawal. To address this, we used propensity score matching (PSM) to minimize bias and achieve balance between groups. PSM is a useful method for controlling confounding, particularly when treatment selection bias is a concern. By creating groups balanced on baseline characteristics, PSM helps minimize bias and can approximate certain aspects of a randomized controlled trial.[24,25] This approach reduces the influence of baseline imbalances, ensuring that differences in outcomes are more directly attributable to the timing of withdrawal rather than underlying differences in patient characteristics. However, its accuracy depends on correctly modeling treatment assignment, because it may not always outperform regression-based approaches if the outcome model is well specified.

To ensure accurate modeling of treatment assignment, we carefully selected clinically relevant covariates and assessed baseline differences between individuals who initiated ASM withdrawal at different postoperative time points (i.e., first, second, third, fourth, or fifth postoperative year) and those who withdrew later. The selection of covariates was informed by our previous work[3], which identified factors associated with seizure relapse after ASM withdrawal after epilepsy surgery. These included the following: age at epilepsy onset, sex, duration of epilepsy before surgery, history of generalized tonic-clonic seizures, number of ASMs at time of surgery, any psychiatric comorbidity, history of febrile seizures, normal presurgical MRI, age at surgery, side of resection, extent of resection, extratemporal (vs temporal) resection, focal preserved consciousness seizures after surgery and before withdrawal, and hippocampal sclerosis on pathology. Covariates such as presurgical intracranial monitoring, postoperative EEG, or MRI were not routinely available and thus were not included.

We used *t* tests for normally distributed data and Wilcoxon rank-sum tests for non-normal data. We then applied PSM using a greedy nearest-neighbor algorithm on the logit of the propensity score, with a caliper width of 0.20–0.25 standard deviations, because this approach minimizes bias more effectively than other matching methods.[19] All covariates listed above were included in the matching process. To evaluate balance between matched groups, we used density plots and standardized mean differences (SMDs), with SMD >0.21 considered indicative of poor balance. This structured approach ensured that differences in outcomes were primarily attributable to the timing of ASM withdrawal rather than baseline imbalances.

We compared time to seizure recurrence between the earlier and later withdrawal groups using the Kaplan-Meier method and log-rank tests before and after matching. We performed leave-one-cohort-out cross-validation to test the consistency of the results across different cohorts. In addition, to demonstrate the stability of the main result in relevant subgroups, we performed sensitivity analyses in those having extratemporal resections, different extent of resections (lesionectomy, lobectomy, or hemispherectomy), and pathology-confirmed hippocampal sclerosis. Within each subgroup, we compared time to seizure recurrence between earlier (first or second postoperative year) and later ASM withdrawal after propensity score matching. Finally, we applied logistic regression in the matched cohorts to estimate the odds of being seizure-free, off ASMs, and in ASM-free remission at the last follow-up.

We followed established recommendations (i.e., Strengthening the Reporting of Observational Studies in Epidemiology checklist). Analyses were performed using R version 1.1.453, using the packages "survival," "survminer," and "MatchIt."

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval for this retrospective, multicenter analysis was obtained from each site's ethics committee or institutional review board (IRB), with participant consent formally waived because all data came from ongoing studies that already had ethical approval and whose data collection was complete or under way. Shiraz University of Medical Sciences IRB approved the Shiraz cohort (91-01-01-5353), and the Bogotá cohort was exempt from IRB review under institutional regulations. No identifiable data or images were obtained or required.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

The registry included 964 individuals (Table 1) from 12 cohorts (London, n = 328; Cleveland, n = 79; Cape Town, n = 96; Brno, n = 86; Shenzhen, n = 75; Lisbon, n = 91; Melbourne, n = 48; Cardiff, n = 38; Shiraz, n = 28; Bogotá, n = 32; Oxford, n = 33; Zurich, n = 30). Of these, 446 (46%) began ASM withdrawal in the first year after surgery, 255 (26%) in the second, 110 (11%) in the third, 58 (6%) in the fourth, 29 (3%) in the fifth, and 66 (7%) later. The median follow-up was 6 years (interquartile range [IQR] 3–11). In total, 334 (35%) experienced seizure relapse (median time to relapse, 4 years [IQR 2–8]). Unadjusted relapse rates by withdrawal timing are listed in Table 2.

After PSM, there were no differences in baseline characteristics between groups (eTable 1). Density plots (eFigure 2) confirmed improved covariate balance in the matched cohorts. Compared with later withdrawal, individuals starting withdrawal in the first (hazard ratio [HR] 1.4; 95% CI 1.1–1.7; $p = 0.003$; Figure 1, panel A2) or second (HR 1.18; 95% CI 1.5–3.0; $p < 0.001$; Figure 1, panel B2) postoperative year had higher seizure relapse risk. Compared with the second year, the smaller HR for those initiating withdrawal

Table 1 Clinical Characteristics

	Overall	First year	Second year	Third year	Fourth year	Fifth year	After fifth year
N Total	964	446	255	110	58	29	66
London	328 (35)	132 (30)	74 (30)	45 (42)	23 (44)	54 (61)	46 (70)
Cleveland	79 (9)	54 (12)	16 (7)	5 (5)	1 (2)	2 (9)	1 (1)
Brno	87 (10)	34 (7)	36 (14)	10 (9)	5 (10)	1 (1)	0 ()
Cape Town	96 (10)	78 (17)	12 (5)	5 (5)	1 (2)	0 (0)	0 (0)
Shenzhen	75 (8)	39 (9)	22 (9)	7 (7)	3 (6)	2 (9)	2 (3)
Lisbon	91 (9)	15 (3)	30 (12)	14 (13)	17 (29)	11 (38)	4 (6)
Melbourne	48 (5)	27 (6)	13 (5)	3 (3)	1 (2)	1 (4)	3 (4)
Cardiff	38 (4)	10 (2)	14 (6)	11 (10)	1 (2)	1 (4)	1 (1)
Shiraz	28 (3)	9 (2)	12 (5)	6 (6)	2 (4)	0 (0)	2 (3)
Bogotá	31 (3)	18 (4)	8 (3)	3 (3)	0 (0)	2 (9)	1 (1)
Oxford	33 (3)	7 (2)	15 (6)	2 (42)	3 (6)	1 (4)	5 (8)
Zürich	30 (3)	24 (6)	4 (2)	0 (0)	1 (2)	0 (0)	1 (1)
Baseline characteristics							
Sex (female)	489 (51)	238 (53)	111 (44)	59 (54)	29 (50)	17 (59)	35 (53)
Age at surgery (y)	34 (26–44)	34 (26–44)	33 (26–44)	32 (24–43)	36 (29–48)	33 (28–42)	34 (27–39)
Age at epilepsy onset (y)	13 (5–21)	13 (5–22)	14 (6–20)	11 (4–20)	12 (6–20)	14 (4–20)	11 (4–18)
Duration of epilepsy at surgery (y)	19 (9–30)	18 (8–29)	18 (10–29)	19 (10–30)	23 (10–31)	24 (13–31)	22 (14–34)
Febrile seizures	302 (36)	127 (31)	75 (36)	40 (41)	17 (39)	5 (30)	38 (61)
Psychiatric comorbidity	254 (30)	103 (26)	67 (30)	31 (32)	22 (44)	8 (38)	23 (38)
Presurgical generalized tonic-clonic seizures	649 (68)	299 (67)	167 (66)	75 (69)	37 (66)	21 (72)	50 (76)
Presurgical seizure frequency per month[a]	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)
Normal MRI	75 (8)	44 (10)	15 (6)	9 (8)	4 (7)	2 (7)	1 (2)
No. of ASMs at surgery	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)
Resection side: left (vs right)	496 (52)	220 (49)	142 (56)	54 (50)	26 (45)	14 (48)	40 (61)
Localization: extratemporal (vs temporal)	366 (38)	210 (47)	89 (35)	30 (27)	13 (22)	7 (24)	17 (26)
Resection extent							
Lesionectomy	337 (38)	139 (36)	103 (43)	41 (39)	27 (47)	16 (59)	11 (17)
Lobectomy	532 (60)	247 (63)	133 (56)	63 (60)	28 (49)	10 (37)	51 (78)
Hemispherectomy	14 (2)	6 (2)	2 (1)	1 (1)	1 (2)	1 (4)	3 (5)
Incomplete resection of lesion[b]	80 (9)	36 (9)	25 (11)	8 (8)	4 (9)	5 (22)	2 (3)
Pathology							
Hippocampal sclerosis	546 (57)	229 (52)	150 (59)	66 (61)	37 (65)	18 (62)	46 (70)
Focal cortical dysplasia	108 (11)	59 (13)	25 (10)	7 (6)	8 (14)	6 (21)	3 (4)
Dysembryoplastic neuroepithelial tumor	58 (6)	31 (7)	16 (6)	4 (4)	3 (5)	0 (0)	4 (6)
Cavernous malformation	61 (7)	28 (7)	10 (4)	7 (7)	4 (7)	4 (15)	8 (12)
Glioma	53 (6)	22 (5)	19 (8)	8 (7)	3 (5)	0 (0)	1 (2)
Dual	61 (7)	26 (6)	16 (7)	6 (6)	8 (14)	4 (15)	1 (2)

Continued

Table 1 Clinical Characteristics *(continued)*

	Overall	First year	Second year	Third year	Fourth year	Fifth year	After fifth year
Other	129 (14)	67 (15)	32 (13)	14 (13)	7 (12)	5 (17)	4 (6)
Normal	24 (2)	15 (3)	7 (3)	2 (2)	0 (0)	0 (0)	0 (0)

Abbreviation: ASM = antiseizure medication.
Data presented as N (%) or median (interquartile range).
[a] Preoperative seizure frequency categorized on an ordinal scale as 0 = no seizures or less than once a year, 1 = at least once a year, 2 = at least once a month, 3 = at least once a week, and 4 = daily seizures.
[b] Incomplete lesion removal was determined when the epileptogenic zone included eloquent areas that were not subject to surgical resection.

during the first postoperative year may reflect the inclusion of only those who were seizure-free for at least 1 year, thus artificially lowering the estimated risks for the first-year group. No significant difference was observed among those initiating withdrawal during the third (HR 1.7; 95% CI 1.0–2.7; $p = 0.14$; Figure 1, panel C2), fourth (HR 1.3; 95% CI 0.5–2.1; $p = 0.45$; Figure 1, panel D2), or fifth (HR 0.17; 95% CI 0.5–1.3; $p = 0.82$; Figure 1, panel E2) year, compared with those who started withdrawal later. Cross-validation using the leave-one-cohort-out approach produced comparable results (eTable 2). HRs before matching can be found in eMethods 2.

We also pooled individuals who began withdrawal during the first or second postoperative year and compared them with those who started later. Consistent with previous findings, early withdrawal was associated with a higher relapse risk (HR 2.2; 95% CI 1.8–2.7; $p < 0.001$; Figure 2). This increased risk persisted when analyses were restricted to individuals with specific characteristics: those with extratemporal resections, hippocampal sclerosis, lesionectomy, or lobectomy. In these subgroups, initiating ASM withdrawal within the first or second postoperative year was associated with a significantly higher risk of seizure recurrence compared with later withdrawal (extratemporal: HR 2.2, 95% CI 1.4–3.17, $p = 0.001$; hippocampal sclerosis: HR 2.2, 95% CI 1.6–3.2, $p < 0.001$; lesionectomy: HR 1.7 95% CI 1.1–2.6 $p = 0.02$; lobectomy: HR 2.2, 95% CI 1.5–3.2, $p < 0.001$). For patients with normal results on pathology (i.e., normal) or those who underwent hemispherectomy, the sample size and event rate were insufficient for reliable Cox model estimation (eFigure 3).

The long-term probability of being seizure-free, off ASMs, or in ASM-free remission at last follow-up did not differ significantly among most withdrawal groups, except for those who withdrew in the second postoperative year, who had lower odds of seizure freedom (risk ratio 0.18; 95% CI 0.90–0.99 $p = 0.04$; Figure 3) but similar rates of complete ASM tapering or being on ASM-free remission.

Discussion

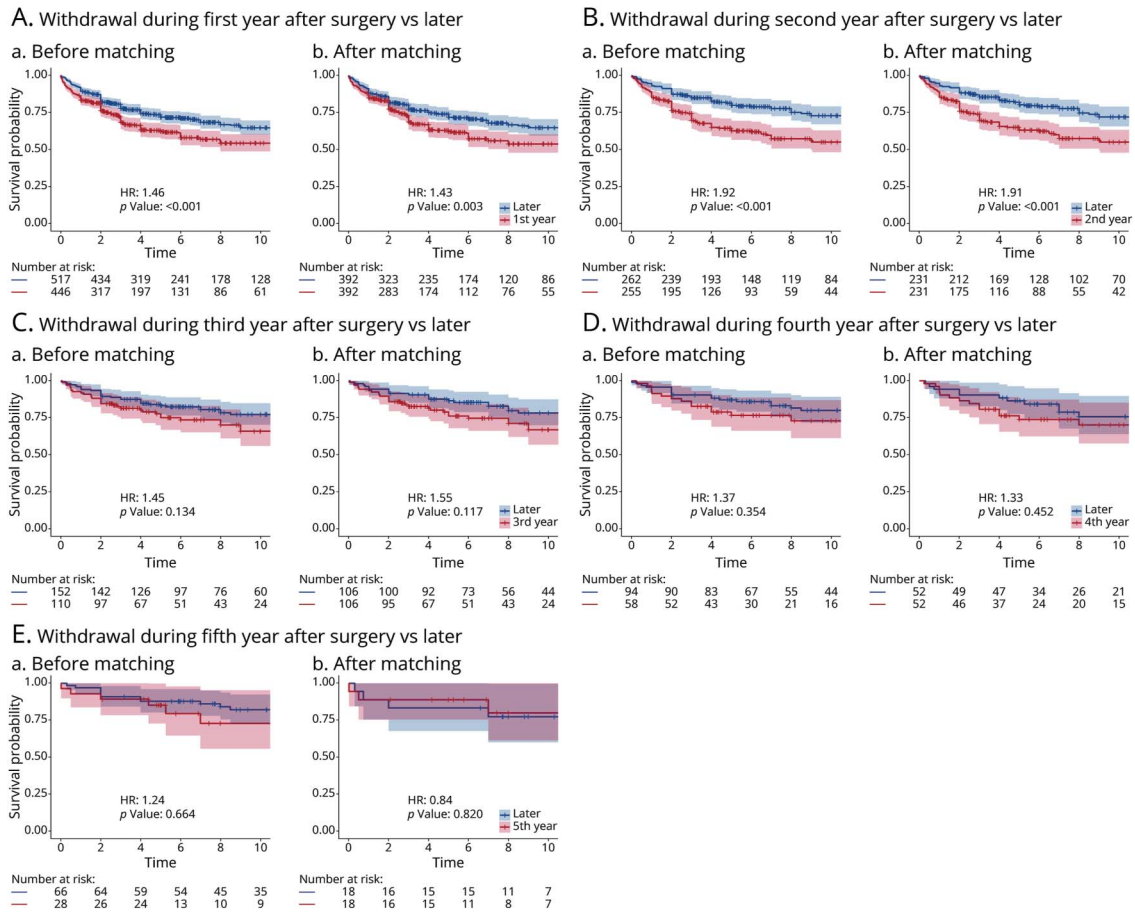
Using a large cohort, we found that, after adjusting for treatment selection bias, initiating ASM withdrawal within the first 2 postoperative years was associated with nearly a doubling of the risk of seizure relapse compared with later withdrawal.

Table 2 Clinical Outcomes

	Overall	First year	Second year	Third year	Fourth year	Fifth year	After fifth year
n	964	446	255	110	58	29	66
Seizure outcomes							
Seizure relapse after starting withdrawal	334 (35)	168 (38)	97 (38)	31 (28)	15 (26)	7 (24)	16 (24)
Time to any seizure relapse (y)	4 (2–8)	3 (2–6)	4 (2–7)	5 (3–9)	6 (4–10)	5 (4–11)	11 (7–17)
Time to begin withdrawal	1 (1–2)	1 (0–1)	2 (1–2)	3 (2–3)	4 (3–4)	5 (4–5)	8 (6–10)
Complete ASM withdrawal at any time point	356 (40)	172 (41)	94 (40)	44 (42)	24 (46)	3 (15)	19 (29)
Follow-up duration	6 (3–11)	5 (3–9)	7 (4–11)	7 (4–11)	8 (5–13)	7 (5–11)	14 (8–19)
Off ASMs at last follow-up	215 (28)	91 (25)	54 (29)	28 (34)	11 (25)	6 (33)	25 (42)
Seizure-free at last follow-up	520 (67)	248 (66)	122 (64)	57 (69)	34 (76)	13 (72)	46 (75)
ASM-free remission at last follow-up	186 (24)	83 (22)	45 (24)	22 (26)	9 (20)	4 (22)	23 (38)

Abbreviation: ASM = antiseizure medication.

Figure 1 Time to First Seizure Relapse After Initiating ASM Withdrawal at Different Time Points



The panels display the Kaplan-Meier curves of the risk of seizure relapse after initiating ASM withdrawal during the first (panel A), second (panel B), third (panel C), fourth (panel D), or fifth (panel E) year after surgery compared with later. The results before propensity score matching are displayed on the left and the findings after matching on the right. ASM = antiseizure medication; HR = hazard ratio.

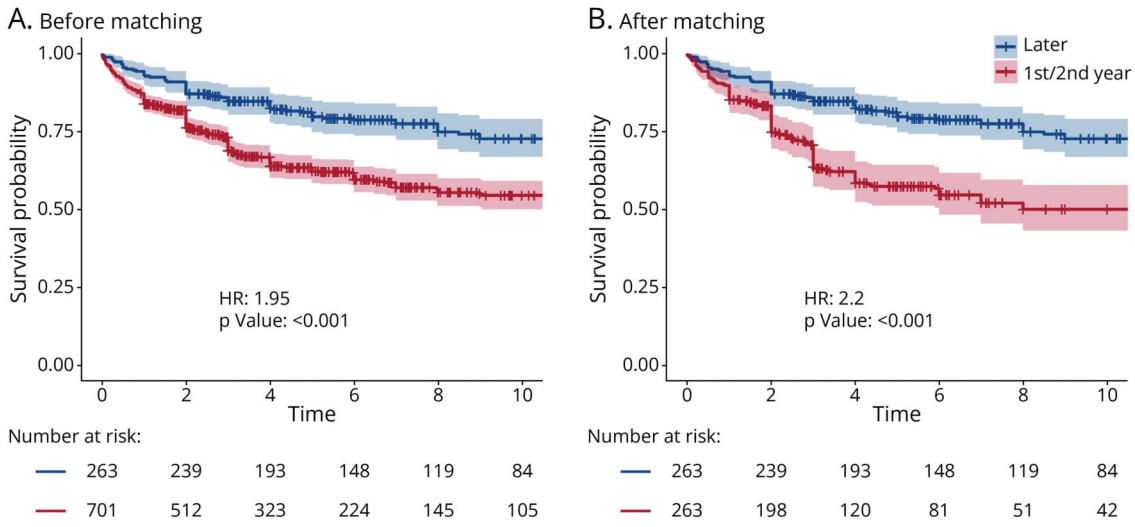
This association remained consistent even in subgroup analyses across key clinical and pathologic characteristics.

Starting withdrawal in the third, fourth, or fifth year showed no increase in relapse risk. These findings suggest that delaying the start of ASM withdrawal beyond 2 years after surgery may not substantially affect early seizure outcomes. Furthermore, the timing of withdrawal did not substantially influence seizure relapse risk, medication use, or ASM-free remission rates at the last follow-up, indicating that long-term outcomes remain unaffected by the timing of starting ASM withdrawal.

The higher immediate seizure relapse risk among people initiating ASM withdrawal earlier likely reflects a shorter "proof" of surgical success. Those who take longer to start withdrawal accrue additional seizure-free time, explaining a lower short-term relapse risk. However, our data suggest that the advantage conferred by a longer seizure-free interval becomes negligible after 2 years.

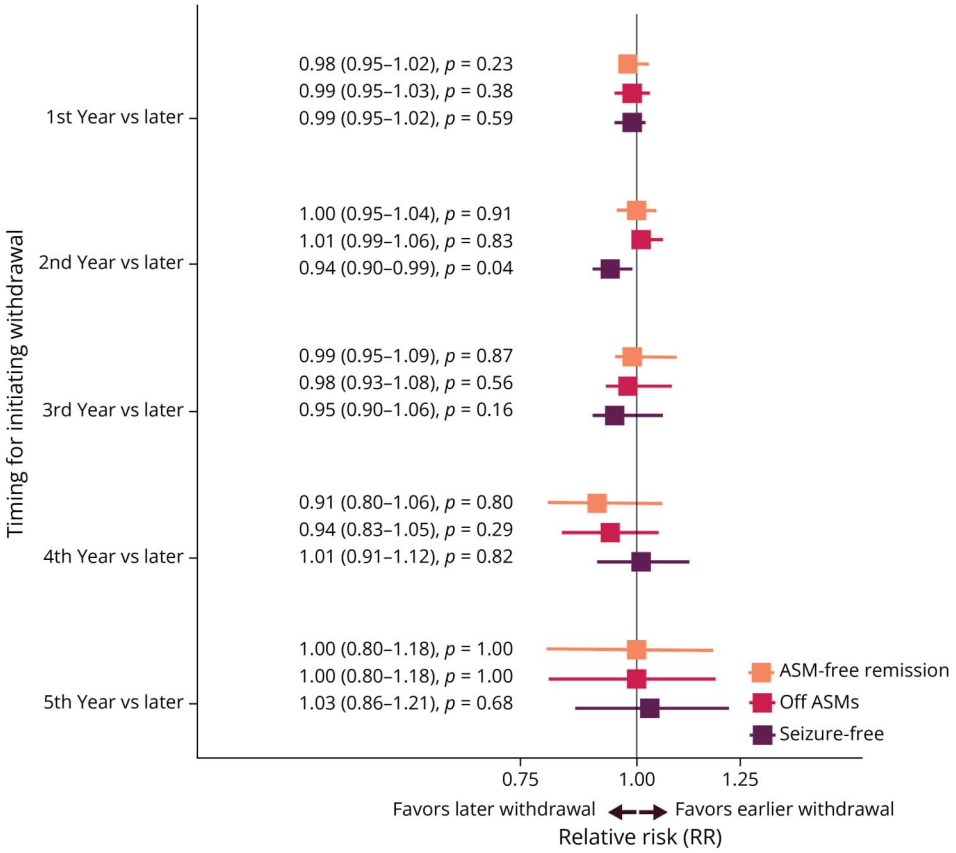
Conversely, clinicians may tend to delay ASM withdrawal in more complex cases at inherently higher risk of relapse, introducing treatment selection bias. To mitigate this, we used PSM to balance disease severity and established risk factors of postoperative seizure recurrence between early and late withdrawal groups. Despite these efforts, PSM cannot address unmeasured factors such as patient or clinician preferences and local practice norms for ASM withdrawal. However, variability in these preferences and protocols introduced a beneficial heterogeneity that allowed for comparisons of diverse withdrawal strategies. As a result, our sample enabled us to evaluate different approaches while controlling for disease severity and inherent seizure risk, partly emulating aspects of a randomized trial. Ideally, a prospective randomized-controlled trial would be conducted to assess these withdrawal strategies definitively, but the associated costs, time, and logistical burden render such a trial impractical. Accordingly, evidence from our well-matched, multicenter, retrospective data set likely represents the most robust data available.

Figure 2 Time to First Seizure Relapse for Withdrawal During the First 2 Postoperative Years vs Later



The panels display the Kaplan-Meier curves of the risk of seizure relapse after initiating ASM withdrawal during the first or second postoperative years vs later. The results before propensity score matching are displayed in panel A and the findings after matching in panel B. ASM = antiseizure medication; HR = hazard ratio.

Figure 3 Long-Term Outcomes After Initiating ASM Withdrawal



The forest plot displays RRs with 95% CIs for the long-term outcomes of ASM withdrawal starting at different time points, vs withdrawal starting later, in the propensity score–matched comparison groups. Long-term outcomes were evaluated during the final year of follow-up and include seizure freedom (purple), medication status (whether ASMs were completely withdrawn; red), and ASM-free remission (people being seizure-free and off ASMs; peach). ASM = antiseizure medication; RR = risk ratio.

Our results have practical implications. Currently, there are no evidence-based guidelines for determining the optimal timing of ASM withdrawal after epilepsy surgery in adults. Our findings suggest that delaying withdrawal beyond 2 years after resective epilepsy surgery offers no significant additional benefit in lowering relapse risk. Conversely, initiating withdrawal during the first 2 postoperative years seems to be associated with a higher likelihood of seizure relapse in the short term, likely related to a shorter "proof" of surgical success. This risk increase was low to moderate and may be acceptable in carefully selected individuals with a low relapse probability. A previously developed prognostic model,[3] supplemented by an online calculator,[7] can be used to assess relapse risk in people considering ASM withdrawal, helping to identify those at lower risk.

Long-term seizure and medication outcomes remained comparable across all withdrawal timings. People who withdrew during the second postoperative year had a marginally significant increase in seizure risk during the final year of follow-up. Still, the relative risk (0.9) was close to 1, indicating minimal differences in long-term seizure freedom. No significant differences were observed for other groups or other long-term outcomes. These findings suggest that even if earlier ASM withdrawal leads to a short-term seizure recurrence, reinstating or adjusting medication typically restores seizure freedom. This highlights an important reassurance for both clinicians and individuals with epilepsy—that a temporary relapse does not necessarily indicate poor long-term prognosis, because resuming treatment can effectively re-establish seizure control. Similar results have been observed after pediatric epilepsy surgery.[18] Thus, earlier withdrawal may help unmask a surgical failure without adversely affecting long-term outcomes.

Our study has several strengths. First, it leverages data from a large international multicenter registry on ASM withdrawal after resective epilepsy surgery. Second, the PSM approach mimics certain aspects of a randomized-controlled trial, minimizing treatment selection bias and refining estimates of the average treatment effect among the treated. Finally, by including all individuals who initiated withdrawal—regardless of whether they completed the taper—our results mimic an "intention-to-treat" analysis rather than reflecting only those who successfully discontinued all ASMs.

Our study has several limitations. The findings apply only to adults undergoing resective epilepsy surgery and may not extend to other populations. Although we matched early and late withdrawal groups on a broad set of clinical variables, unmeasured or unknown confounders—including personal preferences—may still have introduced residual bias. The retrospective design precluded a standardized withdrawal protocol, and follow-up procedures likely varied across centers. The data set reflects diverse withdrawal approaches, ranging from partial dose reductions to complete discontinuation in both monotherapy and polytherapy, limiting conclusions about specific tapering strategies. Owing to variability in data reporting, we were unable to systematically assess how the extent or pace of dose reduction—such as partial vs complete withdrawal—related to seizure recurrence. Our subanalysis of individuals with complete ASM discontinuation at last follow-up addressed this in part, but more granular data on dose reduction trajectories are needed. In addition, the observed differences in HRs across follow-up years may in part reflect diminishing sample sizes over time, which can lead to greater variability and less precise estimates in later years.

Furthermore, we cannot determine whether ASM tapering was initiated with the goal of complete withdrawal or for other reasons, such as minimizing side effects. Nevertheless, the observed seizure outcomes relate to the act of dose reduction itself, irrespective of the underlying clinical rationale. Outcome data were not available for individuals who did not initiate ASM withdrawal. Although this limits direct comparison, it reflects real-world clinical practice across multiple tertiary epilepsy centers and enhances the generalizability of our findings to varied withdrawal protocols. Cross-validation confirmed that our results remained robust across different cohorts. It is important to note that only individuals who initiated withdrawal—presumably those deemed at lower risk of seizure recurrence—were included. As a result, our findings may not apply to patients with higher relapse risk, and we did not include a control group of individuals who continued ASMs without any reduction. Finally, not all cohorts provided detailed information on the specific ASMs used, the presence of epileptiform abnormalities on postsurgical electroencephalography, or the percentage and rate of dose reduction, limiting our ability to adjust for these potentially important factors.

Deciding whether and when to withdraw ASMs after surgery is a shared process among individuals, caregivers, and clinicians. This decision must consider individual preferences, risk of injury, social circumstances (e.g., driving privileges, work capacity, or need for nocturnal supervision), and the clinician's subjective risk assessment. Thus, providing transparent information on the potential risks and benefits is essential. Although retrospective, our findings offer real-world evidence comparing different withdrawal time points. They may be the foundation for developing evidence-based withdrawal protocols, follow-up strategies, and treatment guidelines.

Author Byline *(Continued)*

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