Impact of Antiseizure Medication Taper on Electroencephalographic Dynamics in Focal Epilepsy: a stereo-electroencephalography study

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Antiseizure medication tapering ≠ shifting targets. Seizure-onset localization remains stable during tapering in the EMU. #focal epilepsy #ASM tapering rate #stereo-EEG #electroencephalographic dynamics @AnphyLab

Abstract

Objective: Tapering of the antiseizure medication dosage in the epilepsy monitoring unit can provoke seizures, but its effects on seizure dynamics remain poorly characterized. This study addresses three questions: (1) Does antiseizure medication tapering influence spatiotemporal dynamics of seizures? (2) Does the tapering rate affect these dynamics? (3) Does tapering have a similar effect on interictal epileptic discharges as it does on seizures?

Methods: Patients with drug-resistant epilepsy undergoing stereo-EEG presurgical evaluations at Duke University Medical Center (n=104) and the Montreal Neurological Institute-Hospital (n=80) were screened. We included patients in whom the antiseizure medication dosage was tapered from the highest daily dosage (high-dosage) to ≤50% (low-dosage) during stereo-EEG monitoring, and at least one seizure from the same focus was recorded at both conditions. Using an intra-patient design, we compared seizure-onset zone, onset pattern, and propagation dynamics between the two conditions. Given the intrinsic seizure variability, comparisons were made between same-dosage and cross-dosage seizure pairs. We further assessed effects of tapering rates and examined the characteristics of interictal epileptiform discharges.

Results: Among thirty patients, the proportion of channels in the seizure-onset zone did not differ between high-dosage and low-dosage conditions (7.25% vs 8.95%, p=0.50, d=-0.04). Similarly, no differences were observed in the overlap ratio of seizure-onset regions (62% vs 64%, p=0.72, d=-0.01), or the cross-correlation of seizure-onset patterns (0.36 vs 0.35, p=0.54, d=0.04) when comparing same-dosage versus cross-dosage seizure pairs. Conversely, seizures at low-dosage involved more channels (40.71% vs 81.49%, p=0.001, d=-0.39) and lasted longer (33.36 seconds vs 74.30 seconds, p<0.01, d=-0.47). Tapering rate did not affect seizure dynamics. The mean interictal epileptiform discharge rate and number of propagation channels also remained unchanged.

Significance: Despite seizure exacerbation during antiseizure medication tapering, seizure onset location remained stable. This supports the robustness of seizure-based localization even under reduced medication levels and rapid tapering regimens.

Key words: antiseizure medication taper, tapering rate, stereo-EEG, focal epilepsy, electroencephalographic dynamics

Key points:

- The seizure-onset zone remains spatially stable during antiseizure medication (ASM) tapering, while seizure frequency, propagation and duration increase at low dosage.
- The rate of ASM tapering does not impact localization accuracy.
- The rate and spatial extent of interictal epileptic discharge remain comparable during ASM tapering, but show a vigilance-dependent modulation.

INTRODUCTION

For patients with drug-resistant epilepsy, long-term EEG monitoring in an epilepsy monitoring unit (EMU) is key for guiding surgery.[1] To provoke seizures and shorten stays, ASMs are often tapered. However, how this tapering affects EEG dynamics and seizure architecture remains unclear,[2] limiting refinement of epileptogenic zone (EZ) localization and surgical outcomes.

The seizure-onset zone (SOZ) derived from intracranial EEG is commonly used as a surrogate for the EZ.[3] Early visual analysis has found that ASM tapering does not affect SOZ localization in most cases.[4,5] However, other studies report that the SOZ can expand or appear contralaterally, potentially reflecting an inherently multifocal EZ or complications such as hematoma.[6–8] Furthermore, seizure-onset patterns (SOPs), particularly those with fast activity, are also critical for EZ localization.[9] No study has established whether ASM tapering influences SOP characteristics. Importantly, while mapping seizure propagation is essential for identifying network hubs, the effects of ASM tapering on propagation remain conflicted.[10–12]

The rate of ASM tapering plays a pivotal role in EMU outcomes. Rapid ASM tapering may provoke more frequent focal to bilateral tonic-clonic seizures (FBTC) and seizure clusters, as well as increase the risk of patient falls.[13] Conversely, slow-tapering can prolong patient discomfort and inflate medical costs. Although numerous studies have explored ASM tapering protocols,[13–17] the impact of tapering rate on the spatiotemporal characteristics of seizures remains an important yet unclarified question.

Interictal epileptic discharges (IEDs) are the classical interictal biomarker of epilepsy.[18] Our prior study demonstrated distinct effects of sleep on ictal versus interictal network dynamics in drug-resistant epilepsy,[19] highlighting the value of parallel analyses of these two discharge phenotypes. Extending this framework, comparing the impacts of ASM tapering on seizures and IEDs will comprehensively elucidate the neurophysiological changes induced by ASM tapering in the EMU.

Here, using an intra-patient design comparing seizures at high and low ASM dosages, we quantitatively analyzed spatiotemporal and spectral properties from manual and automated annotations.[20] This study addresses three key questions: (1) Does ASM tapering influence the spatiotemporal dynamics of seizures? (2) Does the rate of ASM tapering affect these spatiotemporal dynamics? (3) Does ASM tapering exert a similar effect on IEDs as it does on seizures? Based on

the literatures, we hypothesize that: (1) ASM tapering does not affect the spatiotemporal dynamics of seizures;[4,5,10] (2) The rate of ASM tapering does not alter seizure dynamics;[16] (3) ASM tapering does not influence spatiotemporal characteristics of IEDs, consistent with previous findings.[21,22]

METHODS

Patient Selection

We screened patients with drug-resistant epilepsy undergoing stereo-electroencephalography (SEEG) presurgical evaluations at Duke University Medical Center (DUMC, 01/2017–04/2025; n=104) and the Montreal Neurological Institute-Hospital (MNI, 06/2013–06/2023; n=80). Daily ASM information (drug, dosage, administration time) was extracted, and a normalized daily drug load score (DLS) was calculated (Figure 1A, Method S1).[23] Inclusion required: (a) ASM load reduced to ≤50% of the highest DLS, and (b) at least one seizure from the same focus recorded at both high (highest DLS) and low (≤50%) dosage. Only seizures during the initial monitoring period were considered "high dosage." Using an intra-patient design, each patient served as their own control. Ethics approvals were obtained at both sites (DUMC Pro0013582, MNI REB IRB00010120).

Intracranial and Scalp EEG Recordings

The DUMC recordings were acquired with Natus Quantum long-term monitoring amplifiers (low-pass filter at 1 kHz with 2048 Hz sampling), using DIXI electrodes. The MNI recordings were acquired with either Harmonie (Stellate, low-pass filter at 500 Hz for 2 kHz sampling, or 70 Hz for 200 Hz sampling) or Nihon-Kohden EEG amplifiers (low-pass filter at 600 Hz for 2 kHz sampling, 70 Hz for 200 Hz sampling), using homemade MNI or commercial DIXI electrodes. Scalp EEG recordings were acquired as in our previous studies.[19] Electrical stimulation was conducted at the end of SEEG monitoring, following the full resumption of ASMs.

Selection of EEG Segments

Seizure Epochs

All SEEG-recorded seizures were classified as high or low dosage based on normalized DSL. Because seizure properties were shown to be independent of the vigilance state,[19] vigilance stage was not considered. The seizures at the low dosage were taken from the lowest available ASM dosage. If seizures with two or more distinct foci were recorded in each patient, seizures with the same epileptic focus were selected to enable comparison between the two dosages. Due to a discrepancy in the number of seizures between the two dosage conditions, up to three seizures per condition were selected, with a preference given to seizures with more severe clinical manifestations.

In seizure clusters (≥3 seizures within a 2-hour period), only the first seizure of each cluster was included.

Interictal Epochs

A 30-minute epoch of the interictal SEEG was selected from high- and low-dosage conditions. Because IED characteristics change across different vigilance states,[19,24] we selected interictal epochs from both wakefulness and non-rapid eye movement sleep (NREM) separately. Epochs were selected ≥2 hours away from focal preserved consciousness seizures (FPC) and focal impaired consciousness seizures (FIC),[25] and ≥12 hours away from FBTC.

Analysis of Seizures

Seizure Marking

For each selected seizure, SEEG channels were reviewed in a bipolar montage and marked by an epileptologist. Seizure onset was defined as the first sustained rhythmic EEG change distinct from the background, and offset as the end of this activity,[26] often followed by postictal suppression.[19]

Co-registration of SEEG Contacts

The 3D coordinates of SEEG contacts were determined by co-registering pre-implantation MRI with post-implantation CT scans, followed by manual labeling of the SEEG contacts. These contacts were then mapped to a standardized MNI space and registered to the Automated Anatomical Labeling 3 (AAL3) brain atlas containing 166 regions.[27] This mapping was performed by considering a 5 mm spherical region centered at the midpoint between each bipolar channel pair. Channels outside the brain, in the white matter or with artifacts were excluded.

Seizure-onset Pattern

To account for inter-seizure variability,[28] we compared SOP similarity between same-dosage and cross-dosage seizure pairs using cross-correlation analysis.[19] SEEG signals were downsampled to 200 Hz and bandpass-filtered (0.3-70 Hz). From each seizure, a SOP epoch (defined as 5.1 s epoch starting at onset) was extracted.[9] Cross-correlation values were computed between all channel pairs derived from the paired epochs (high-high, low-low or high-low dosage). To mitigate variability in expert annotation of seizure onset, we used the maximum cross-correlation coefficient between two epochs, which identifies the optimal match between the SOPs. If multiple seizure pairs were available for a given patient, mean cross-correlation values (for both the first and all channels) were

computed to generate a single representative value per patient, which was then compared between the same-dosage and cross-dosage groups.

Spatiotemporal Propagation of Seizures

We calculated the percentage of SEEG channels involved at seizure onset (first 500 ms) and throughout the entire seizure, relative to the total number of implanted electrodes. Furthermore, we compared the regional overlap of the SOZ between same-dosage and cross-dosage seizure pairs. To evaluate whether clinical characteristics (time difference between seizure onsets at high and low dosages, age, epilepsy duration, receiving long half-life ASMs, focus location, lesion presence and aetiology) influenced the change in the percentage of channels in SOZ between high and low dosage, we performed a multiple linear regression analysis (Method S2). Temporal propagation was quantified using seizure duration and latency to maximal channel involvement. SEEG channels were grouped into ≤500 ms propagation clusters based on activation timing (Figure 1B).[19] The number of clusters reflected stages of spatial spread, while the mean interval between clusters captured temporal dynamics.

Epileptogenicity Index

The Epileptogenicity Index (EI), which quantifies the emergence of ictal high-frequency activity (12-97 Hz) and its latency relative to seizure onset, was used to evaluate the spectral characteristics of seizures using the AnyWave EI plugin, developed at the Aix-Marseille University.[20,30] The EI was computed on all involved SEEG channels and normalized for each seizure. Seizures lacking fast activity were excluded. Given that multiple seizures were recorded per ASM dosage condition, the mean EI value across all seizures from the same dosage was calculated to account for inter-seizure variability. The percentage of channels with high epileptogenicity (EI ≥0.3),[20] relative to the total number of involved channels, was compared across dosages. Then the mean correlation of EI across all channels between seizures within the same ASM dosage and across different ASM dosages were computed and compared, aiming to assess spatial EI variability across channels.[19]

To visualize brain regions with high epileptogenicity, SEEG channels were grouped according to a reduced version of the MICCAI atlas comprising 38 regions.[31] Additionally, Pearson's correlation was used to assess whether the similarity in EI distribution across involved SEEG channels differed significantly between same-dosage and cross-dosage seizure pairs.

Effect of ASM Tapering Rate on Seizures

Given that different ASMs have distinct absorption and elimination half-lives, we utilized a pharmacokinetic model based on ASM load to estimate blood plasma levels (BPL, Method S3).[23] This approach was chosen over the DSL to accurately capture the temporal dynamics of tapering. Fast-tapering was defined as a reduction in BPL exceeding 60% within the first two days, while reductions of ≤60% constituted slow-tapering.[13] To quantify change ratio of features across dosage levels for each tapering group, the difference in values between low and high dosages was calculated and normalized to the value at the high dosage. Subsequently, we compared the change ratio of seizure frequency and spatiotemporal features between the fast- and slow-tapering groups.

Comparative Analysis of IEDs and Seizures

IEDs were automatically detected in the selected interictal SEEG epochs using a validated detector.[32] The IED rate was defined as the number of IEDs per minute in each channel. IED propagation was measured by counting channels with IEDs occurring within 120 ms of a source IED.[33] For each dosage condition, we calculated the mean IED rate and number of propagation channels per patient. Intra-patient comparisons were performed to account for interpatient differences in IED rate and spatial distribution. We then compared the spatial overlap of highest IED-rate channels (top 10%) and SOZ between high-dosage and low-dosage conditions. A higher overlap percentage reflects greater spatial consistency. Furthermore, overlap was also assessed using IED-γ, a validated biomarker that was shown to be more specific for the EZ than traditional spikes.[32]

Statistical Analysis

All features were tested for normality using the one-sample Kolmogorov–Smirnov test. As the data were not normally distributed, the nonparametric two-tailed Wilcoxon signed-rank (for paired samples) or rank-sum test (for independent samples) was applied. A false discovery rate correction was implemented, and effect sizes are presented using Cliff's Delta (d) values.[34] Feature values are presented as median (interquartile range/IQR), unless otherwise specified. Fisher's exact test was used to compare seizure and SOP types between two dosage conditions. All statistical analyses were performed using MATLAB 2020b (MathWorks, Santa Clara, CA, USA) with a significance level of $\alpha=0.05$.

RESULTS

Thirty patients (11 from DUMC and 19 from MNI) were included (Figure S1). Patient demographics are listed in Table S1.

Seizure Frequency Increases during ASM Tapering

The change of seizure frequency during ASM tapering is shown in Figure S2. No substantial differences were observed in the number of seizures across individual ASMs or their combinations. At the low-dosage condition, the median daily seizure count was significantly higher than at the high-dosage condition ($p=0.03$, $d=-0.26$; Table 1, Figure S3). Both clinical and subclinical daily seizure counts showed similar significant increases at the low-dosage condition. Among clinical seizures, all seizure types showed increased daily counts during tapering, but only FPC reached statistical significance ($p=0.03$, $d=-0.24$). None of the 30 patients in our cohort exhibited non-habitual seizures.

A total of 140 seizures were manually marked on every involved SEEG channel and analyzed across all patients: 63 from the high-dosage condition and 77 from the low-dosage condition. The number of foci between two groups has no significant difference ($p=1.00$, $d=0.00$). The mean count of seizures per patient for analysis was 2.10 ± 0.80 for high and 2.57 ± 0.68 for low dosage. Fisher's exact test revealed a significant difference in seizure type distribution between dosages ($p<0.001$), with subclinical seizures being less frequent at the lower dosage.

Cross-dosage Variability in SOPs is Not Greater than Same-dosage Variability

SOPs at the low-dosage followed a similar distribution to those that occurred during the high-dosage condition ($p=0.60$, Figure S4A and B). Same-dosage and cross-dosage SOPs cross-correlations were analyzed, with one patient excluded due to insufficient seizures for same-dosage computation. In the remaining patients (n=29), the peak cross-correlation of the SOP from the first involved channel in the seizure did not differ significantly between same-dosage (0.25, IQR=0.26) and cross-dosage conditions (0.26, IQR=0.16; $p=0.57$, $d=0.03$; Figure S4C). Likewise, when considering all common channels involved in the SOP in each seizure combination, the peak same-dosage (0.36, IQR=0.16) and cross-dosage cross-correlation (0.35, IQR=0.18) were not significantly different ($p=0.54$, $d=0.04$; Figure S4D).

SOZ Remains Stable while Seizure Duration and Spread Rise during ASM Tapering

Visual assessment of the channels involved in seizure onset across SEEG channels did not reveal obvious differences between ASM dosages (Figure 2A). However, both seizure duration and the number of propagated channels increased substantially at low dosage. The proportion of channels involved in the SOZ did not differ significantly between high and low dosage ($p=0.50$, $d=-0.04$; Table 1 and Figure 2B). For regional variability analysis of the SOZ, two patients were excluded due to incomplete data, including one without valid MNI coordinates, and the other one only having one seizure per dosage. As a result, 28 patients were included in the final analysis. The mean spatial overlap ratio of SOZ regions in same-dosage seizure pairs (62%, IQR=26%) did not differ significantly from that in cross-dosage seizure pairs (64%, IQR=37%; $p=0.72$, $d=-0.01$; Figure 2C). Variance in the change in SOZ channel percentage was not adequately explained by the investigated predictors, reflected by a non-significant overall regression model ($F=0.79$, $p=0.62$). Furthermore, none of the individual predictors showed a significant association with the change in SOZ channel percentage (all $p>0.05$) (Table S2).

Conversely, the percentage of SEEG channels involved in the entire seizure was significantly increased at low dosage compared to high dosage ($p=0.001$, $d=-0.39$; Figure 3A). The mean overlap ratio of seizure regions in cross-dosage seizure pairs (75%, IQR=48%) was significantly lower than that in same-dosage seizure pairs (90%, IQR=33%, $p=0.001$, $d=0.35$; Figure 3B). This finding demonstrated that the spatial variability of seizures between high and low dosages is much greater than that among seizures at the same dosage. Seizure duration at low dosage was significantly increased compared to high dosage ($p<0.01$, $d=-0.47$; Figure 3C). This was also true for the total number of clusters ($p<0.01$, $d=-0.41$; Figure 3D). However, there was no significant difference between dosages in the percentage of latency to maximal activation ($p=0.98$, $d=-0.06$; Figure 3E), nor the mean time interval between the onset of consecutive propagation clusters ($p=0.57$, $d=-0.09$; Figure 3F). Similar trends were observed for both clinical and subclinical seizures (Table S3).

Epileptogenicity of Seizures Varies More across ASM Dosage Conditions than within the Same Dosage

Eleven of 30 patients (37%) did not exhibit consistent high-frequency activity during seizures at either high and/or low ASM dosage and were therefore excluded from this analysis. The EI is known to be insensitive to SOPs characterized by slower frequency activity, which accounts for 20-30% of

commonly observed SEEG patterns.[35] Among the remaining patients (n=19), the energy ratio heatmaps and visual inspection of brain regions with high EI did not reveal obvious differences between different dosages (Figure S5A and B). However, a subtle increase in epileptogenicity was observed in non-SOZ channels at the lower dosage. The proportion of channels with high epileptogenicity did not differ significantly between low and high dosage (high: 7.69%, IQR=12.12%, low: 8.04%, IQR=23.34%; p=0.16, d=0.14; Figure S5C). When computing the Pearson's correlation of EI distributions across SEEG channels under same-dosage and cross-dosage conditions, two additional patients were excluded due to having only one seizure at high dosage and one seizure at low dosage, which prevented same-dosage comparisons. In the remaining patients (n=17), the cross-dosage correlation of EI values (0.68, IQR=0.40) was significantly decreased compared to same-dosage (0.8, IQR=0.26; p=0.02, d=0.25; Figure S5D), suggesting greater variability in EI distribution across different ASM dosages.

Seizure Frequency and Dynamics are not Affected by the ASM Tapering Rate

Based on the rate of ASM tapering (Figure 4A), 10 patients were categorized into the fast-tapering group and 20 into the slow-tapering group. There was no significant difference in the change ratio of daily seizure count (p=0.75, d=0.14) and FBTC (p=0.75, d=-0.06) between the fast-tapering and slow-tapering groups (Figure 4B and C). Six patients in the slow-tapering group were given lorazepam in the EMU. When comparing the change ratio of channels in the SOZ between fast-tapering and slow-tapering groups, there was no significant difference (p=0.86, d=0.37; Figure 4D). Similarly, the change ratio in the number of channels involved in entire seizures between the two groups was not significantly different (p=0.86, d=-0.20; Figure 4E). Regarding the change in spatiotemporal seizure characteristics between the fast-tapering and slow-tapering groups, no significant differences were observed in seizure duration (p=1.00, d=0.02; Figure 4F), number of clusters (p=0.86, d=-0.15; Figure 4G), normalized latency to maximal activation (p=0.86, d=-0.14; Figure 4H), or mean time interval between onset of clusters (p=0.86, d=-0.15; Figure 4I).

Changes in IEDs with ASM tapering

Because suitable interictal epochs with a sufficient interval from seizures at the specified ASM dosages were not available in some patients, only 27 patients with a total of 134 epochs were included in the analysis. During wakefulness, the mean IED rate did not differ between the high (1.98, IQR=3.43) and the low dosage (1.79, IQR=2.29, p=0.94, d=0.02; Figure 5A). Similarly, the

mean number of IED propagation channels showed no difference (high: 2.34, IQR=1.3, low: 2.44, IQR=0.82; p=0.94, d=-0.06). During NREM sleep, the mean IED rate (high: 4.19, IQR=4.04, low: 3.90, IQR=4.08; p=0.70, d=-0.01) and number of propagation channels remained comparable across dosages (high: 3.39, IQR=1.85, low: 3.46, IQR=1.47, p=0.70, d=-0.11).

The spatial overlap of channels between high and low dosages was significantly higher for SOZ (50.00%, IQR=33.70%) than for the highest IED-rate channels during wakefulness (25.00%, IQR=41.53%; p=0.02, d=-0.49; Figure 5B), but not different from that during NREM sleep (50.00%, IQR=36.15%; p=0.97, d=0.02). Interestingly, the overlap of highest IED-rate channels was greater during NREM sleep than wakefulness (p=0.02, d=0.46). However, this difference was not observed when comparing the overlap of highest IED-rate channels between wakefulness and NREM sleep across different dosages (Figure S6A). IED-γ showed similar results (Figure S6B and S7).

For the regional-level analysis, two additional patients were excluded for the same reason as in the SOZ regional variability analysis. The subsequent results mirrored those observed at the channel level. The spatial overlap of regions across dosages was significantly higher for SOZ (85.71%, IQR=55.00%) than for the highest IED-rate channels during wakefulness (50.00%, IQR=29.17%; p=0.03, d=0.49; Figure 5C), but not significantly different from that during NREM sleep (62.50%, IQR=39.55%; p=0.41, d=0.18). The regional overlap of highest IED-rate channels was greater during NREM sleep than wakefulness (p=0.03, d=0.28).

DISCUSSION

Despite widespread use of ASM tapering in pre-surgical evaluation, evidence on its effects remains limited. We systematically assessed seizure dynamics, tapering rate, and interictal activity across dosages. Key findings were: (1) SOZ localization is stable, though seizures become more frequent, prolonged, and widespread at low dosage; (2) tapering rate does not influence seizure dynamics; and (3) interictal activity is stable across dosages but varies with vigilance. Thus, ASM tapering alters seizure dynamics without disrupting SOZ localization.

SOZ Remains Stable but Seizure Severity Increases during ASM Tapering

Case reports have suggested ASM tapering may enlarge the SOZ,[6,36] but our quantitative analysis demonstrated that SOZ distribution and epileptogenic channels were consistent across dosages at the group level.[11,37] In addition, variability at the individual patient level could not be explained by clinical characteristics such as time difference between seizure onsets at high and low dosages, age, epilepsy duration, receiving long half-life ASMs, focus location, lesion presence and aetiology. This stability supports the view that once the EZ surpasses a critical threshold, seizures consistently arise from the same SOZ regardless of dosage or vigilance state.[19,38] Current models propose that epileptic seizures originate from dysfunction of specific microcircuits within the SOZ, which then progressively recruit other microcircuits to activate the entire seizure network.[39] The inherent dysfunction in specific circuit component (e.g., a synapse or neuron) of the microcircuit either through gain- or loss-of-function (e.g., change in synaptic strength or intrinsic excitability) may account for the robustness and persistence of the SOZ, even under varying pharmacological conditions. Specifically, the receiving of long-half-life ASMs did not affect the change in the percentage of SOZ channels between high- and low-dosage conditions. None of our patients exhibited non-habitual seizures, though such events have been described in temporal epilepsy, often linked to bilateral or multifocal abnormalities rather than tapering itself.[4–8,40]

Importantly, while the SOZ remained unchanged, seizures at low dosage were longer and more widespread, with reduced cross-dosage epileptogenicity correlation and broader network activation. These findings align with prior work showing ASM suppresses propagation by limiting excitatory transmission or targeting regions critical for spread,[11,12,41] whereas tapering permits broader cortical–subcortical recruitment and prolonged seizures.

Seizure Frequency Increases during ASM Tapering

In our study, daily seizure counts increased at low dosage, consistent with prior reports.[11,12] Both clinical and subclinical seizures increased, likely due to a lowered seizure threshold.[42] The nucleus-shell model suggests partial seizures originate from a pacemaker (nucleus) and propagate to produce ictal signs in the first (FPC/FIC) and second (FBTC) shells.[12] Indeed, our findings suggest that the tapering of ASM does not predominantly influence the range of the seizure's pacemaker but instead acts especially on the propagation of seizure activity. Although no significant difference in FBTC was seen, a trend toward increased generalization was noted.

Tapering Rate of ASM Does Not Influence SOZ Features

Our study systematically compared detailed SEEG-based spatiotemporal metrics of the SOZ and seizure propagation under different tapering rates. Critically, we accounted for the considerable variability in ASM half-lives by using BPL curves to model ASM load[43] instead of relying on DSL alone. Moreover, our patient cohort was drawn from two independent epilepsy centers. Our results demonstrated that the frequency and spatiotemporal changes in seizures from high to low ASM dosage did not significantly differ between the fast- and slow-tapering groups. It is noteworthy that one-third of the patients experienced a reduction in BPL of more than 60% within two days, while the remaining two-thirds showed less than 60% reduction over the same period. This suggests that the overall tapering process was relatively gradual.

We found no significant difference in seizure severity between fast- and slow-tapering groups, consistent with prior retrospective work.[16] This is in contrast to a prospective study suggested more frequent 4-hour seizure clusters with fast tapering.[13] Interestingly, in our study, the use of rescue medication consistently occurred in the slow-tapering group, suggesting an intrinsic predisposition of certain patients to develop seizure clusters, rather than an effect driven by the rate of ASM reduction. Although rapid discontinuation has been linked to rebound seizures,[37] we observed no such effect; instead, seizures in fast-tapering patients appeared several days after reduction, indicating a delayed response. It is important to note that tapering protocols for both groups did not abruptly withdraw ASMs.

IED Rates and Propagation are not Modulated by ASM Tapering

IED rates and propagation did not differ between high and low ASM dosages in either wakefulness or NREM. This aligns with reports of stable IED rates across medication levels,[21,22] though others noted paradoxical decreases or rebounds.[44–47] They speculate that IEDs represent an inhibitory mechanism within the epileptic network. When the medication dosage is reduced, this inhibition is weakened, leading to a decrease in IED frequency. By selecting interictal segments well separated from seizures, we minimized confounding effects of recent seizures on interictal activity. We also observed that IED distribution varied more in wakefulness than NREM, consistent with prior work showing more IEDs during sleep.[19,24] This likely reflects high neural synchronization during NREM,[24,48] limiting further ASM effects. In summary, the vigilance state exerts a stronger influence on IED characteristics than ASM dosage, while SOZ localization remains stable.

Clinical Implications

Our findings show that SOZ distribution is consistent across ASM dosages, indicating that seizures during tapering retain equal localizing value. Tapering rate did not affect seizure features, and daily ASM reductions >30% seem therefore safe, supporting personalized accelerated tapering to shorten hospital stays. Finally, spatial IED extent was more stable during NREM sleep than wakefulness across medication dosages, reinforcing its role as the preferred state for identifying the EZ, in line with previous studies.[49]

Strengths & Limitations

This study had three strengths: (1) multicenter data to enhance generalizability; (2) a quantitative approach for rigorous investigation of ASM tapering effects; and (3) an intra-patient, same/cross-dosage design for patient heterogeneity and seizure variability. The main limitation was the absence of actual daily ASM blood levels as not feasible in clinical routine. To mitigate this potential weakness, we modeled ASM drug metabolism values. Also, patient numbers did not allow us to investigate dosage effects within specific epilepsy subtypes. Third, all patients received highly variable medication combinations across the cohort, not allowing the isolation of the individual effects of specific ASMs or their respective mechanisms of action on seizure dynamics.

CONCLUSION

SOZ distribution remains stable during ASM tapering, though seizures become longer and more widespread when ASM dosages is lower. Since tapering rate does not affect seizure features, EZ localization is reliable across tapering strategies. Of note, differences in IED characteristics across dosages vary more in wakefulness than in NREM, indicating that NREM may provide a more robust basis for EZ identification and surgical planning.

AUTHOR CONTRIBUTIONS

G.R., S. H., J.T., J.G., and B.F. contributed to the conception or design of the work; K.S., M.M., T.A., A.H., D.S., J.H., and R.R. played major role in the acquisition of data; G.R., S.H., J.T., K.J., X.W., N.G., E.C., J.G., and B.F contributed to analysis and interpretation of data; G.R., S.H., J.T., H.Y., X.S., Q.W., and B.F. contributed to drafting and revision critically for important intellectual content. All authors have read and approved this manuscript.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon reasonable request for participating patients who agreed to open data sharing when consenting to this research.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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FIGURE LEGENDS

Figure 1. Study design flowchart and schematic of seizure analysis methods. (A) Study design flowchart. To standardize antiseizure medication (ASM) dosage across patients, a normalized daily drug load score (DLS) was calculated. Daily seizure counts as well as seizure-onset characteristics were then reviewed in patients undergoing stereo-electroencephalography (SEEG). Patients were included if at least one seizure originating from the same epileptic focus was recorded at both the high (the highest DLS after SEEG initiation) and low dosage conditions (≤50% of the highest dosage). For each dosage condition, a maximum of three seizures, and one 30-minute interictal epoch during wakefulness and non-rapid eye movement (NREM) sleep were analyzed. Spatiotemporal characteristics of seizures and interictal activities, as well as the effect of ASM tapering rate on seizure dynamics were compared between high-dosage and low dosage conditions. **(B)** Clusters in a seizure were defined as groups of SEEG channels that became involved in the seizure within a 500-ms window (yellow rectangle). Seizure onset was marked on each involved channel in a bipolar montage (red circles). Two channels from each of the first three propagation clusters (Clusters 1, 2, and 3) are shown. The time intervals between the onset of consecutive propagation clusters were calculated to quantify the temporal dynamics of seizure evolution. In this example, T1 represents the interval between Clusters 1 and 2, and T2 represents the interval between Clusters 2 and 3.

Figure 2. Seizure-onset zone (SOZ) remains stable while seizure duration and spread increase during ASM tapering. **(A)** Top: An example of a focal preserved consciousness seizure (FPC) at high ASM dosage. The patient exhibited bilateral tonic jaw contraction and mouth opening. These motor symptoms resolved at seizure termination, after which the patient took a deep breath and remained fully conscious throughout. SEEG recordings revealed a tonic discharge originating from the right middle insula and precentral gyrus (red rectangle) and remained in these regions (blue rectangle), with a duration of approximately 15 seconds. Bottom: An example of a FPC in the same patient at low dosage. In addition to bilateral tonic jaw contraction, the patient displayed prolonged clonic movements of the left face and head. The seizure onset remained localized to the right middle insula and precentral gyrus (red rectangle); however, it subsequently propagated to the right frontal and parietal operculum, middle frontal gyrus, anterior insula, posterior cingulate gyrus, and supramarginal gyrus (blue rectangle). The total duration of the seizure was 47 seconds. **(B)** The

percentage of channels involved in SOZ did not differ significantly between low and high dosage (p=0.50, d=-0.04). **(C)** The mean overlap ratio of SOZ regions in same-dosage seizure pairs did not differ significantly from that in cross-dosage seizure pairs (p=0.72, d=-0.01). R=right; SOZ=seizure-onset zone; Outliers are plotted based on 1.5×interquartile range.

Figure 3. Seizure duration and spread increase during ASM tapering. (A) The percentage of channels involved in the entire seizure was significantly higher at low dosage (p=0.001, d=-0.39). **(B)** The mean overlap ratio of seizure regions across different dosages was significantly lower than that observed within the same dosage (p=0.001, d=0.35). **(C)** Seizure duration was significantly longer at the low ASM dosage compared to the high dosage (p<0.01, d=-0.47). **(D)** The total number of clusters was also significantly greater at the low dosage (p<0.01, d=-0.41). **(E)** In contrast, there was no significant difference in the normalized latency to maximal activation between the two dosage conditions (P=0.98, d=-0.06). **(F)** Similarly, the mean time interval between the onset of consecutive propagation clusters did not differ significantly between dosage conditions (p=0.57, d=-0.09). Outliers are plotted based on 1.5×interquartile range. ***p≤0.001, **p<0.01.

Figure 4. Seizure dynamics are not affected by the tapering rate of ASM. (A) The top four curves represent the modeled blood plasma levels (BPLs) for each ASM; the bottom curve shows the corresponding mean values. On the bottom curve, the decrease of BPL was larger than 60% in two days, so this patient was classified into the fast-tapering group. **(B)** The change ratio in daily seizure count from high to low dosage did not differ significantly between the fast-tapering and slow-tapering groups (p=0.75, d=0.14). **(C)** Similarly, no significant difference was observed in the change ratio of daily FBTC count between the two groups (p=0.75, d=-0.06). **(D)** The change ratio in the number of SOZ channels was also comparable between groups (p=0.86, d=0.37). **(E)** Likewise, the change ratio in seizure channel count showed no significant group difference (p=0.86, d=-0.20). **(F–I)** There were no significant group differences in the change ratio of seizure spatiotemporal characteristics: seizure duration (**F**; p=1.00, d=0.02), cluster count (**G**; p=0.86, d=-0.15), latency to maximal activation (**H**; p=0.86, d=-0.14), and mean time interval between cluster onsets (**I**; p=0.86, d=-0.15). Outliers are plotted based on 1.5×interquartile range.

Figure 5. Alterations in interictal epileptic discharges (IEDs) during ASM tapering and comparison with seizure-onset zone. (A) IED: During wakefulness, the mean IED rate across all

SEEG channels showed no significant difference between low-dosage and high-dosage conditions ($p=0.94$, $d=0.02$; first panel). Similarly, the mean number of IED propagation channels did not differ significantly ($p=0.94$, $d=-0.06$; second panel). During non-rapid eye movement sleep (NREM) sleep, both the mean IED rate ($p=0.70$, $d=-0.01$; third panel) and the number of propagation channels ($p=0.70$, $d=-0.11$; fourth panel) remained unchanged across dosage levels. **(B)** At the channel level, the spatial overlap between high and low dosages was significantly higher for SOZ than for the top 10% highest IED-rate channels during wakefulness ($p=0.02$, $d=0.49$), but not significantly different from that during NREM sleep ($p=0.97$, $d=0.02$). Interestingly, the overlap of highest IED-rate channels was greater during NREM sleep than wakefulness ($p=0.02$, $d=0.46$). **(C)** Similarly, at the regional level, the spatial overlap between dosages conditions was significantly higher for SOZ than for top 10% highest IED-rate channels during wakefulness ($p=0.03$, $d=0.49$), while no significant difference was found when compared with that during NREM sleep ($p=0.41$, $d=0.18$). Interestingly, the regional overlap of highest IED-rate channels was greater during NREM sleep than wakefulness ($p=0.03$, $d=0.28$). W=wakefulness. Outliers are plotted based on 1.5×interquartile range. *$p\leq0.05$.