Clinical commentary

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Rapid antiepileptic drug withdrawal may obscure localizing information obtained during presurgical EEG recordings

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ABSTRACT – Withdrawal of antiepileptic drugs (AEDs) is a standard procedure during presurgical epilepsy assessment. Rapid and, at times, even pre-hospital withdrawal of medication is performed in some centres to enhance the yield of recorded seizures during video-EEG monitoring. AED withdrawal, however, affects the propensity and speed of propagation of epileptic activity, may evoke more severe seizures, and may cause pitfalls in EEG interpretation. We report a case which had been recommended to undergo intracranial EEG recordings in order to clarify apparently discordant MRI findings and ictal EEG patterns when monitoring was performed following complete AED withdrawal. Re-evaluation to assess scalp EEG patterns at several drug levels during slow AED tapering showed a loss of localizing information with AED withdrawal due to contralateral and bitemporal spread of frontal epileptic activity. Our report demonstrates that in individual cases, rapid AED withdrawal during presurgical video-EEG monitoring can impair the validity of EEG recordings and lead to unnecessary risks and investigations during workup.

Key words: antiepileptic drug, AED, withdrawal, video-EEG, tapering, presurgical workup, localization

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Withdrawal of antiepileptic drugs (AEDs) is considered an efficient way to precipitate seizures in order to decrease recording times during presurgical work-up. The clinical and electrophysiological alterations due to AED withdrawal have been investigated in a relatively small number of studies with controversial results. Whereas some reports suggest a minor effect on clinical semiology and EEG (Marciani and Gotman, 1986; Gotman and Koffler, 1989; Marks *et al*., 1991), others provide evidence of changes in electrographic seizure propagation (Zhou *et al*., 2002) and changes in ictal or interictal EEG

findings as well as seizure semiology (Ludwig and Marsan, 1975; Engel and Crandall, 1983).

Here, we report effects of rapid AED withdrawal in a patient who was considered to have discordant EEG findings with a suspected epileptogenic left frontal lesion, and was thus offered intracranial recordings to clarify the relationship between ictal EEG and imaging data. Analysis of scalp EEG at slower AED tapering speed revealed obscuring effects during rapid AED tapering.

Case study

A 20-year-old male presented for a second opinion at our epilepsy centre following presurgical evaluation in another hospital. His epilepsy had manifested at the age of 16 with bilateral tonic-clonic seizures without aura, as well as focal seizures with impaired awareness and manual automatisms, resistant to drug treatment with levetiracetam (LEV) and lacosamide (LCM). Presurgical evaluation at the external centre

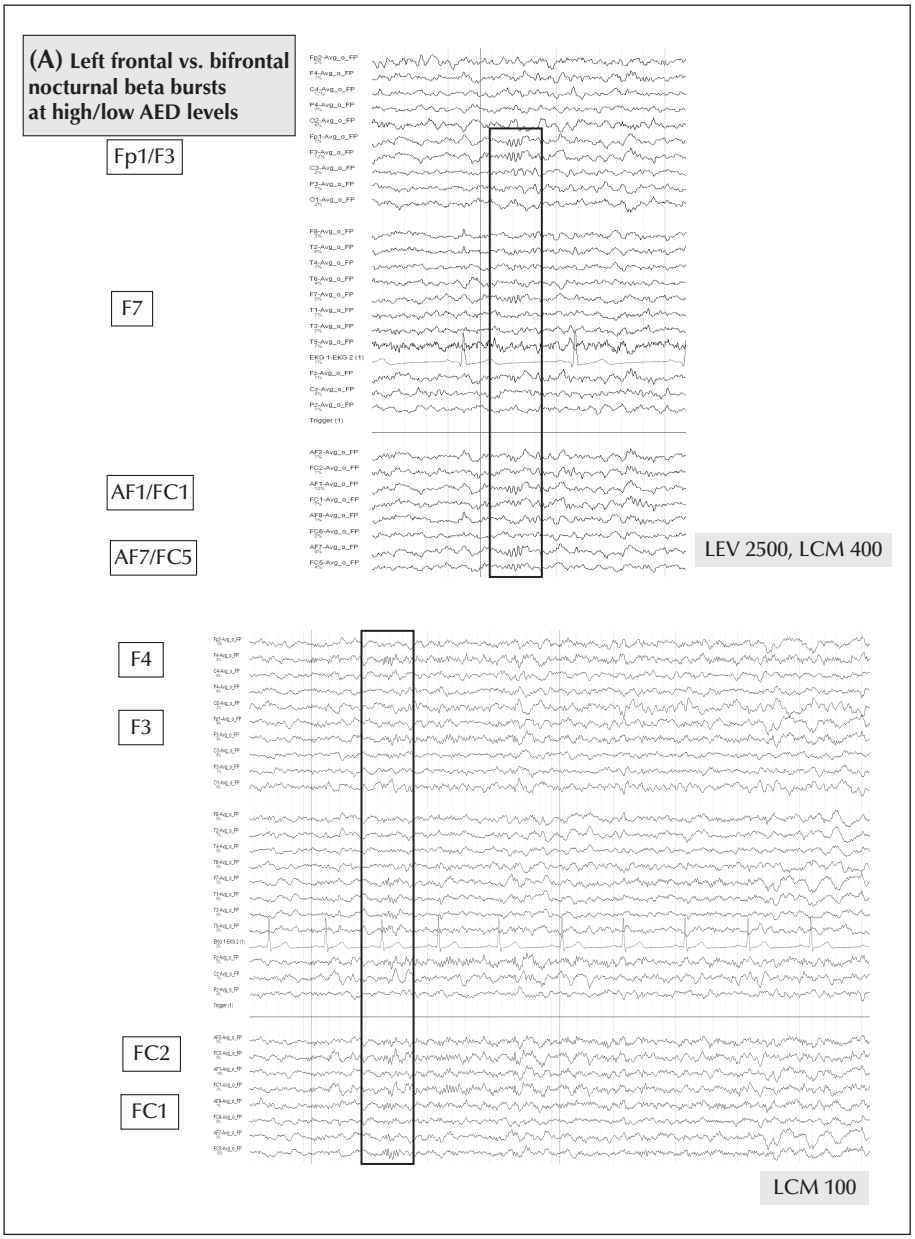

Figure 1. Changes in interictal EEG events (A, B) and ictal patterns (C, D) depending on the level of antiepileptic drugs.
Note the initial left frontal localization of interictal and ictal EEG discharges at high medication load and the following bifrontal and bitemporal distribution of those at lower medication.
All recordings are presented with common average montage. LEV: levetiracetam; LCM: lacosamide.

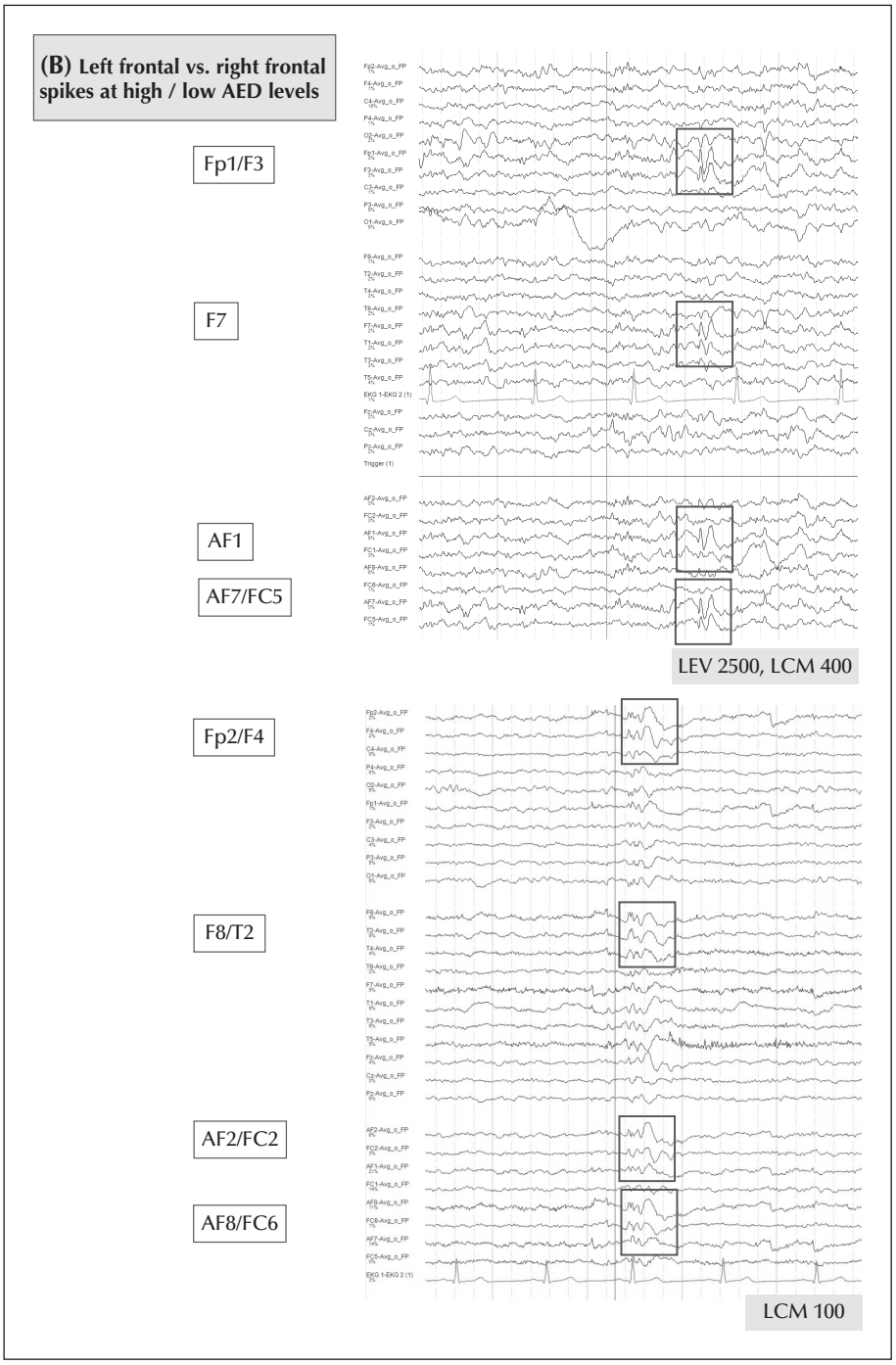

Figure 1. Changes in interictal EEG events (A, B) and ictal patterns (C, D) depending on the level of antiepileptic drugs (*continued*).

was performed after complete AED withdrawal and had shown bifrontal or even bitemporal patterns with right-sided predominance. Due to the unclear localization or even discrepant findings on scalp EEG, an additional invasive examination was advised to ascertain a relationship between the lesion and the epileptic seizures.

To clarify this issue, an additional video-EEG recording was performed for one week with closely spaced frontal and central scalp electrodes in addition to the standard 10-20 system. Baseline medication of LEV (3,000 mg/d) was gradually tapered by 500 mg per day while maintaining LCM (400 mg/day) until Day 6, with tapering thereafter.

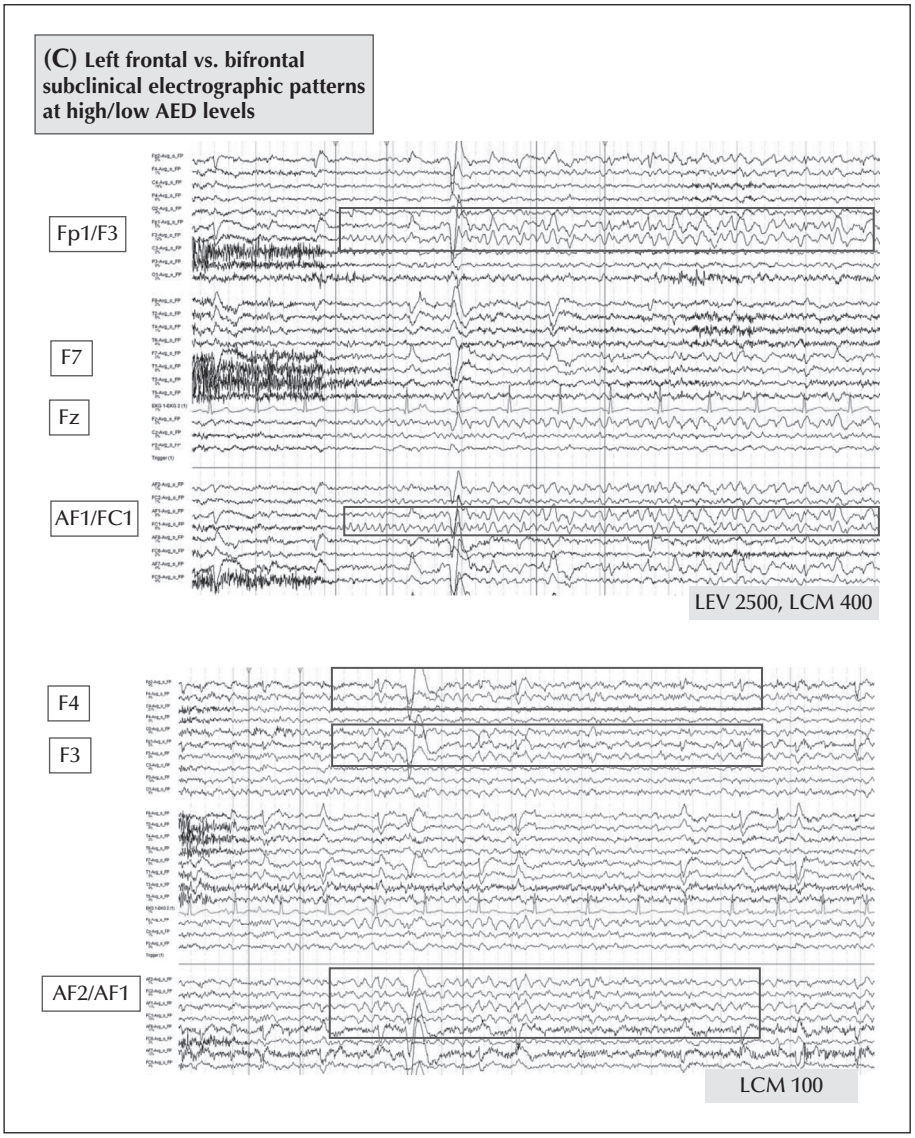

Figure 1. Changes in interictal EEG events (A, B) and ictal patterns (C, D) depending on the level of antiepileptic drugs (*continued*).

Both interictal and ictal patterns showed major alterations during the period of AED tapering. Whereas initially, at high AED levels, interictal sharp waves and beta bursts as well as subclinical electrographic seizure patterns were recorded, concordant with the lesion, they became bifrontal with sometimes even contralateral accentuation (*figure 1A-D*); a decrease of ipsilateral spiking was observed from 70% to 40% in both pre- and postictal phases (*supplementary table 1*).

At high AED levels, only one mild nocturnal seizure occurred which was detected only later upon re-evaluation of video-EEG recordings. With progressive AED withdrawal, ictal patterns during clinically manifesting seizures showed more rapid propagation to both temporal lobes, with only minor initial patterns remaining visible over the left frontal epileptogenic region. These propagation patterns following drug tapering thus resembled the externally recorded patterns with unclear lateralizing and localizing information.

The recorded seizure semiology did not show any significant changes in localizing or lateralizing aspects during AED withdrawal. Focal seizures with impaired awareness and oral and left manual automatisms were documented, progressing twice to bilateral tonic-clonic seizures with head version to the right.

Based on EEG recordings obtained at higher drug levels, MRI, and seizure semiology, the evidence was considered sufficient to perform epilepsy surgery without additional intracranial recordings. Following

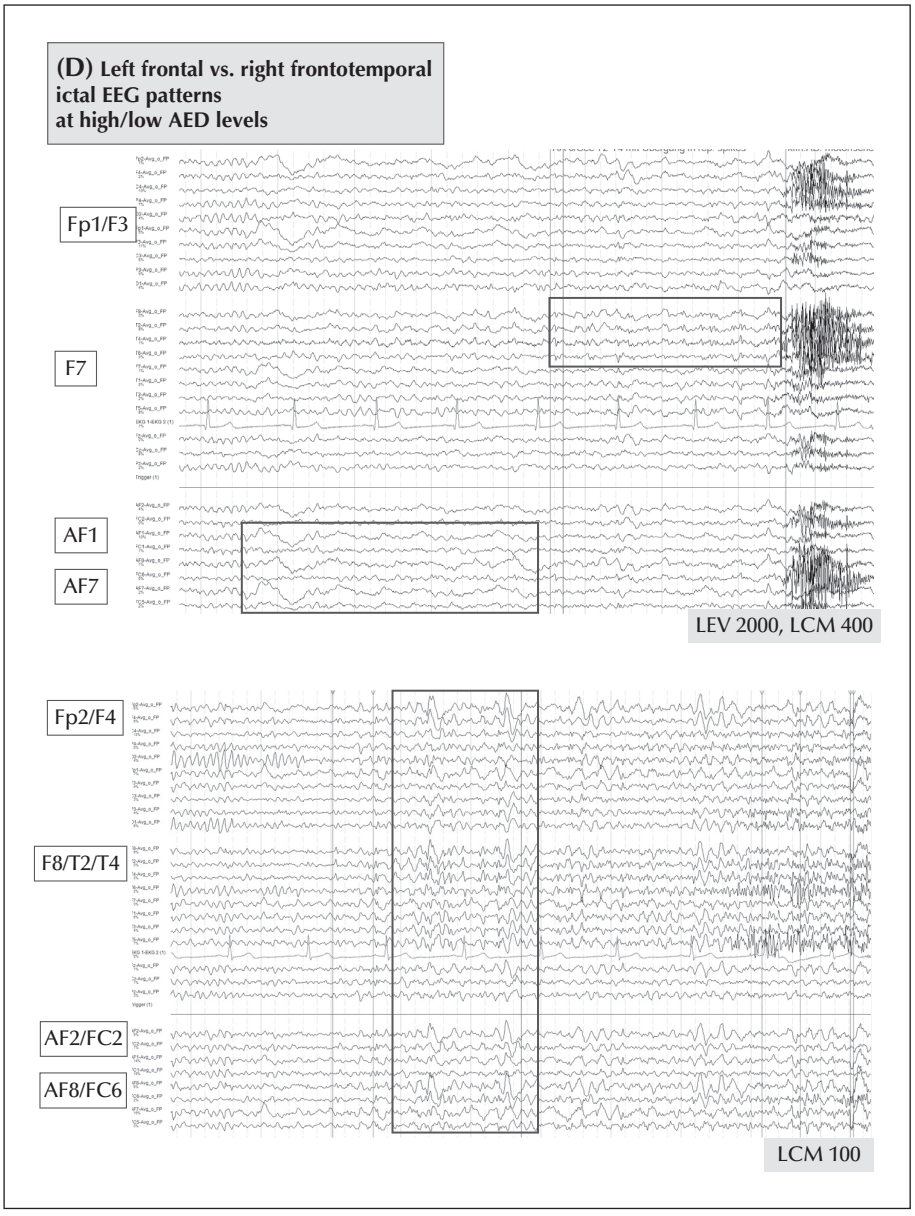

Figure 1. Changes in interictal EEG events (A, B) and ictal patterns (C, D) depending on the level of antiepileptic drugs (*continued*).

left frontal lesionectomy (*figure 2*), the patient has so far been seizure-free for a follow-up period of one year.

Discussion

Withdrawal of AEDs during presurgical evaluation is a standard, yet non-standardized, procedure aimed at provoking seizures (Jehi, 2016). It is assumed that seizures recorded during AED tapering are considered valid for localizing the epileptogenic zone (Andersen *et al*., 2010). Although AED withdrawal is known to increase the risk of severe seizures (Zhou *et al*., 2002) and SUDEP (Williams *et al*., 2006), rapid AED withdrawal has been recommended (Rizvi *et al*., 2014; Al Kasab *et al*., 2016) and sometimes even started prior to hospital admission without monitoring for patient safety in order to shorten the length of time in hospital (Jehi, 2016), mainly for economic reasons.

The rational for timing and speed of antiepileptic medication withdrawal has mostly been discussed with regards to its potential to compromise patient safety. Here, we show that rapid AED withdrawal may also cause critical localizing and lateralizing information to be overlooked due to widely extended EEG patterns in

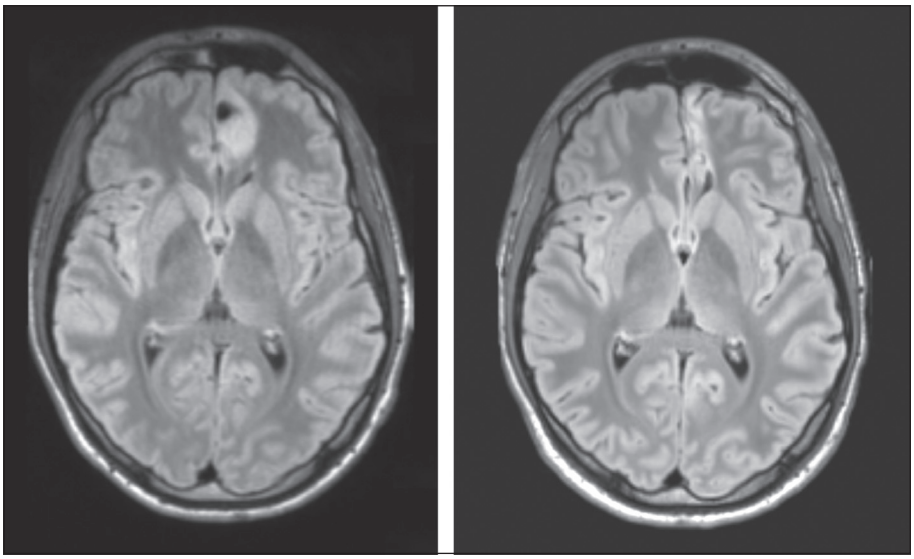

Figure 2. Preoperative MR flair image (left) shows a low-grade glial tumour on the medial surface of the left frontal lobe. Postoperative MR image (right) shows complete removal of the tumour with residual non-specific reactive gliosis. Histology corresponded to dysembryoplastic neuroepithelial tumour, WHO Grade I.

areas including the contralateral hemisphere and distant brain areas, resulting in discordant findings during presurgical workup which could lead to unnecessary and costly additional procedures.

In accordance with this observation, in one of the first reports of EEG changes during medication termination, a previous, relatively localized epileptic focus was shown to become "diffusely" spread after the anticonvulsant medication was abruptly terminated (Ludwig and Marsan, 1975). Similarly, AED withdrawal has been shown to increase the number of sleep-associated bitemporal interictal epileptiform discharges in patients with unilateral hippocampal sclerosis (Doležalová *et al*., 2014). Also, falsely lateralizing ictal onsets during anticonvulsant drug withdrawal were reported in a patient who underwent bilateral stereotaxic EEG. Since the patient became seizure-free after unilateral temporal lobectomy, the seizures originating from the contralateral side were considered to be the result of anticonvulsant withdrawal (Engel and Crandall, 1983).

Supposedly, AEDs contribute to a focal restriction of epileptic discharges, both interictally and during seizure onset, whereas their withdrawal leads to a change in localization or more diffuse epileptic discharges. The observed patterns more likely represent electrographic propagation of focal epileptic activity to distant brain regions, indistinguishable from primary generators on scalp-EEG, rather than a sequential involvement of different potentially epileptogenic structures. Seizure control resulting from the left frontal lesionectomy in the presented case confirms this assumption. Therefore, a false impression of multifocality may arise if EEG analysis is performed only after medication withdrawal. This may be even more critical in non-lesional cases or in patients with post-traumatic (Irimia and Van Horn, 2015) or postencephalitic (Singh *et al*., 2015) aetiology of epilepsy, which is frequently associated with widespread brain damage.

Despite the fact that AED withdrawal is generally not considered to influence electrographic seizure onset (Marks *et al*., 1991; Andersen *et al*., 2010), the above described case illustrates that AED withdrawal can cause activation of cortical areas beyond the epileptogenic zone or extended spread of primarily focal discharges, and thus compromise presurgical workup due to falsely localizing information. As there are few similar reports in the literature, such cases may be rare, and a case series is required to draw conclusions regarding systematic features. At present, it seems reasonable to consider EEG patterns both with and without antiepileptic drug exposure, since this can provide relevant and complementary localizing information due to the effect of AED reduction on the degree of propagation of interictal and ictal discharges. □

Supplementary data.

Summary didactic slides and supplementary table are available on the www.epilepticdisorders.com website.

Disclosures.

None of the authors have any conflict of interest to declare.

References

Al Kasab S, Dawson RA, Jaramillo JL, Halford JJ. Correlation of seizure frequency and medication down-titration rate during video-EEG monitoring. *Epilepsy Behav* 2016; 64: 51-6.

Andersen NB, Alving J, Beniczky S. Effect of medication withdrawal on the interictal epileptiform EEG discharges in presurgical evaluation. *Seizure* 2010; 19: 137-9.

Doležalová I, Brázdil M, Hermanová M, Janoušová E, Kuba R. Effect of partial drug withdrawal on the lateralization of interictal epileptiform discharges and its relationship to surgical outcome in patients with hippocampal sclerosis. *Epilepsy Res* 2014; 108: 1406-16.

Engel Jr. J, Crandall PH. Falsely localizing ictal onset with depth EEG telemetry during anticonvulsant withdrawal. *Epilepsia* 1983; 24: 344-55.

Gotman J, Koffler DJ. Interictal spiking increases after seizures but does not after decrease in medication. *Electroencephalogr Clin Neurophysiol* 1989; 72: 7-15.

Irimia A, Van Horn JD. Epileptogenic focus localization in treatment-resistant post-traumatic epilepsy. *J Clin Neurosci* 2015; 22: 627-31.

Jehi L. Antiepileptic drug management in the epilepsy monitoring unit: any standards? *Epilepsy Curr* 2016; 16: 116-7.

Ludwig BI, Marsan CA. EEG changes after withdrawal of medication in epileptic patients. *Electroencephalogr Clin Neurophysiol* 1975; 39: 173-81.

Marciani MG, Gotman J. Effects of drug withdrawal on location of seizure onset. *Epilepsia* 1986; 27: 423-31.

Marks DA, Katz A, Scheyer R, Spencer SS. Clinical and electrographic effects of acute anticonvulsant withdrawal in epileptic patients. *Neurology* 1991; 41: 508-12.

Rizvi SA, Hernandez-Ronquillo L, Wu A, Téllez Zenteno JF. Is rapid withdrawal of anti-epileptic drug therapy during video EEG monitoring safe and efficacious? *Epilepsy Res* 2014; 108: 755-64.

Singh TD, Fugate JE, Hocker SE, Rabinstein AA. Postencephalitic epilepsy: clinical characteristics and predictors. *Epilepsia* 2015; 56: 133-8.

Williams J, Lawthom C, Dunstan FD, *et al*. Variability of antiepileptic medication taking behaviour in sudden unexplained death in epilepsy: hair analysis at autopsy. *J Neurol Neurosurg Psychiatry* 2006; 77: 481-4.

Zhou D, Wang Y, Hopp P, *et al*. Influence on ictal seizure semiology of rapid withdrawal of carbamazepine and valproate in monotherapy. *Epilepsia* 2002; 43: 386-93.

TEST YOURSELF

(1) What risks are associated with rapid AED withdrawal?

(2) How does AED tapering affect localization and lateralization of ictal EEG patterns?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".