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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

# Predictors of focal to bilateral tonic-clonic seizures during long-term video-EEG monitoring

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**Abstract**

**Objective:** To determine predictors of focal to bilateral tonic-clonic seizures (FBTCS) during video–electroencephalography (EEG) monitoring (VEM).

**Methods:** All adult patients undergoing presurgical VEM from 2014 to 2015 in the department of epileptology were eligible (N = 229). Those with refractory focal epilepsy and epileptic seizures recorded during VEM were analyzed (N = 188, Group 1). To assess the effects of antiepileptic drug (AED) taper, the total AED load was calculated as the sum of the ratios of prescribed daily dose and defined daily dose of all AEDs per VEM day and was correlated with the occurrence of focal seizures without bilateral tonic-clonic seizures (FwoBTCS) and FBTCS. To validate the findings, data of patients undergoing VEM in 2004 and 2005 (Group 2, eligible N = 243, analyzed N = 203) were also investigated.

**Results:** In Group 1, 53 patients had FBTCS and 135 patients had exclusively FwoBTCS during VEM. Reduced AED load at seizure onset was the most important modifiable risk factor for FBTCS (receiver-operating characteristic [ROC]: area under the curve [AUC] = 0.78). Furthermore, the risk of FBTCS varied with the history and frequency of FBTCS prior to VEM. For instance, patients had a 50% risk of FBTCS by reducing the AED load to ~20% when no information about history of FBTCS was taken into account, to ~30% when a positive history of FBTCS was taken into account, and to ~50% when a high frequency of FBTCS prior to VEM was taken into account. These findings were largely replicated in Group 2 (59 patients with FBTCS and 144 exclusively with FwoBTCS).

**Significance:** The risk of FTBCS during VEM depends on the history and frequency of FTBCS prior to VEM and is particularly associated with the extent of AED reduction. Our data underscore the need for appropriate tapering regimens in VEM units.

**KEYWORDS**

antiepileptic drugs, assessment for epilepsy surgery, patient safety

# 1 | INTRODUCTION

Video–electroencephalography (EEG) monitoring (VEM) is a widely used method in the diagnostic assessment for epilepsy surgery. To facilitate the occurrence of focal seizures, it is common practice in epilepsy-monitoring units (EMUs) to taper off antiepileptic drugs (AEDs). At present, specific protocols for AED load reductions are lacking in most epilepsy centers.[1,2] During VEM, a proportion of 24%-57% of patients develop focal to bilateral tonic-clonic seizures (FBTCS).[3] Some semiologic signs (eg, forced deviation of head and eyes contralateral to the putative hemisphere of seizure onset) during FBTCS may provide additional information in the presurgical assessment. However, FBTCS are usually not intended, as they are associated with significant risks to patients' safety. Seizure-related falls occur in 1%–20% of patients in EMUs, sometimes with severe injuries due to FBTCS.[4–6] Furthermore, FBTCS are associated with apnea and subsequent hypoxemia, in some cases leading to bradycardia, asystole, and sudden unexpected death in epilepsy (SUDEP).[7,8] Although FBTCS in EMUs are likely to be detected earlier than in other environments, they are nonetheless a major source of complications. Therefore, it would be of considerable value to identify factors that modify the risk of their occurrence.

We hypothesize that the risk of FBTCS during VEM is influenced by the patients' history and frequency of previous FBTCS and, more importantly, by AED load reduction. To investigate these hypotheses, various individual and clinical factors as well as daily AED doses were retrospectively assessed in two groups of patients who underwent VEM for the evaluation of epilepsy surgery.

**Key points**

- Potential risk factors of focal to bilateral tonic-clonic seizures (FBTCS) during video–electroencephalography (EEG) monitoring (VEM) were investigated.
- Important predisposing factors were history and frequency of FBTCS prior to VEM.
- The antiepileptic drug (AED) load reduction was the most important modifiable risk factor for FBTCS during VEM.
- The risk of potentially deleterious FBTCS might be reduced by appropriate AED tapering regimens according to the individual seizure history.

# 2 | METHODS

## 2.1 | Study design and population

The study investigated risk factors for FBTCS during VEM in two cohorts of patients, assessed for possible epilepsy surgery in an EMU, separated by one decade. Strengthening the reporting of observational studies in Epidemiology criteria for case-control studies, the RECORD statement for observational studies using routinely collected health data, and the STARD list for reporting diagnostic accuracy studies were applied, according to the EQUATOR reporting guidelines (available at http://www.equator-network.org, accessed 12/10/2019).

We primarily investigated consecutive adult (≥18 years) patients with refractory focal epilepsy who had seizures during VEM in the EMU of the University Hospital Bonn, Germany, Department of Epileptology in the years 2014 and 2015. In a second step, patients of 2004 and 2005 were also analyzed, to test the reliability of our results. All patients who underwent VEM for presurgical assessment in the respective periods were examined for eligibility. The standard battery of presurgical assessment includes cerebral magnetic resonance imaging (MRI), VEM using noninvasive scalp EEG or invasive EEG, and neuropsychological testing. In VEM, live video is constantly recorded to correlate patient's behavior and semiological signs with the regional onset and propagation of seizure activity. Patients with idiopathic generalized epilepsy syndromes or psychogenic nonepileptic seizures only were excluded. We also excluded patients with incomplete data records, patients without any seizure during VEM, and multiple cases of the same patients to guarantee meaningful statistical analysis. Furthermore, patients were excluded who did not take any AED at all or AED without available defined daily dose (DDD) values. In addition, patients whose seizures could not be categorized as FwoBTCS or FBTCS were excluded.

## 2.2 | Outcome measures

Patients with focal without bilateral tonic-clonic seizures (FwoBTCS) only during VEM served as controls for patients with at least one FBTCS during VEM. The AED load for each day during VEM was assessed as the sum of the ratios of prescribed daily dose (PDD) per DDD for all AEDs of the patient, allowing for interindividual comparisons of total drug loads, irrespective of specific combinations of substances.[9] The DDD for individual AEDs are published by the World Health Organization (WHO) and are accessible online.[10–13] Age, sex, type of EEG recording, history of FBTCS, frequency of FBTCS (with "high frequency" being defined as occurrence of at least one FBTCS within the last 3 months prior to VEM, or an average of at least one FBTCS per 3 months over the last 12 months prior to VEM and clusters over one day being treated as one seizure), MRI lesions, localization of seizure onset, state of vigilance at seizure onset, the AED load at VEM start and at the time point of the first FwoBTCS or first FBTCS (absolute and relative to VEM start), as well as the velocity of AED reduction to first seizure (relative change of AED load per day) were assessed (Table S1). Status epilepticus was not an outcome measure and we did not assess history of status epilepticus as a possible risk factor for FBTCS.

### 2.3 | Data and statistical methods

Medical records were reviewed and relevant data were extracted and pseudonymized. The investigators had full access to the data of all patients. Possible bias might arise from tapering regimens that were not standardized but depended on the individual decisions of the treating physicians. Furthermore, tapering regimens might have been different for specific types of AED. To circumvent these sources of bias, we analyzed data from two patient groups separated by one decade with other treating physicians and an expectedly different distribution of AED. The study size was determined by the number of patients investigated with the method of VEM during the respective time intervals. Analyses were performed using IBM SPSS 25. Group statistics compared patients who had FwoBTCS only (a) with those who developed at least one FBTCS (b) during VEM, using Student's $t$ tests and $\chi^2$ tests (or Fischer's exact tests) at a significance level of $\alpha = 0.05$. Furthermore, receiver-operating characteristic (ROC) and hierarchical logistic regressions were calculated for specific predictors. In ROC, the area under the curve (AUC) determines the accuracy of the respective predictors. In the logistic regression, the expected value of the binary variable "Occurrence of FBTCS" is regressed on the logistic function of a linear combination of predictors. Thereby, the linear combination of predictors is mapped to the interval from 0 to 1, and thus the predicted value denotes the probability that an FBTCS occurs:

$$P(\text{“Occurrence of FBTCS”}) = \exp(\beta_0 + \beta_1 X_1 + \dots + \beta_k X_k) / [1 + \exp(\beta_0 + \beta_1 X_1 + \dots + \beta_k X_k)].$$

The regression model's fit is indicated by the deviance, which under the null hypothesis follows a $\chi^2$ distribution with $k$ (number of predictors) degrees of freedom. In the same vein, a significant difference in deviance between nested models indicates that the additional predictors in the more complex model critically contribute to the prediction of the dependent variable. Averaged group data are given as mean ± SD.

This retrospective audit of data collected during standard clinical care was approved by the local medical ethics committee (Ethikkommission an der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn, No. 352/12).

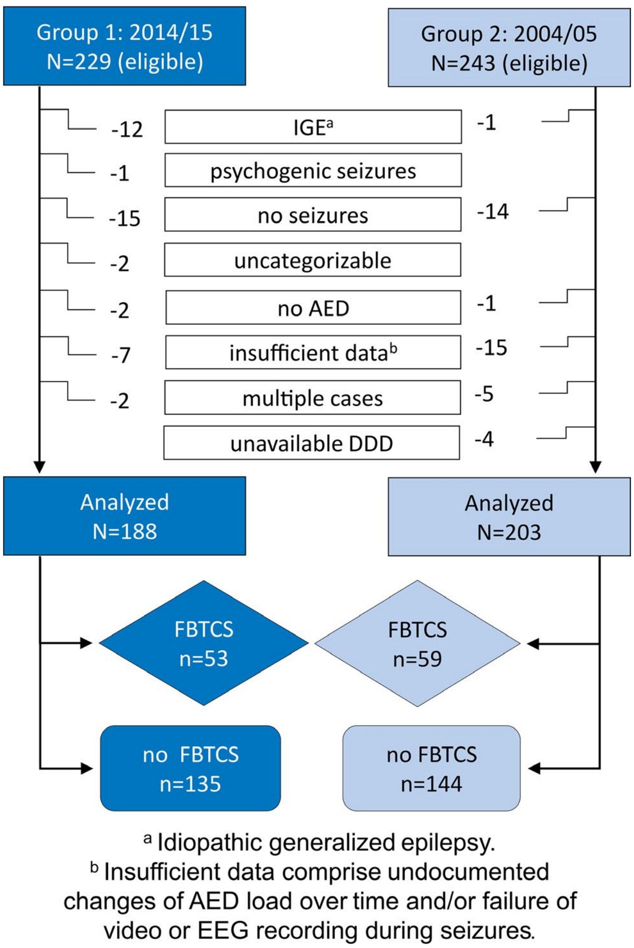


**FIGURE 1** Inclusion and exclusion criteria

## 3 | RESULTS

### 3.1 | Study population

In a first step, 229 adult patients undergoing VEM for pre-surgical assessment in the years 2014 and 2015 were examined for eligibility (Figure 1). A total of 188 patients were included in the final analysis (Group 1), of whom 53 had FBTCS (subgroup 1b, absolute AED load at VEM start = 3.03 ± 1.10) and 135 exclusively FwoBTCS (subgroup 1a, absolute AED load at VEM start = 3.58 ± 1.58) during VEM, resulting in 2.55 controls per case. In a second step, 243 adult patients who underwent presurgical assessment 10 years before (years 2004 and 2005) in the same EMU were also analyzed (Group 2). A total of 203 individuals were included in the final analyses of Group 2, comprising 59 patients with FBTCS (subgroup 2b, absolute AED load at VEM start = 2.49 ± 1.38) and 144 with only FwoBTCS during VEM (subgroup 2a, absolute AED load at VEM start = 2.79 ± 1.63), which equals 2.44 controls per case. Group 1 and Group 2 did not differ significantly in age ($t = -1.50$, $df = 389$, ns), or sex

($\chi^2$ = 0.82, $df$ = 1, ns), yet distribution of specific AED was significantly different, Fisher's exact test = 99.86, $df$ = 25, $P \leq .001$ (Figure S1).

## 3.2 | Predictors of FBTCS during VEM: Receiver-operating characteristics

Predictors were only considered reliable if their values were significantly different in the seizure-type–related subgroups (a and b) of both patient groups (1 and 2). Univariate analyses revealed that "Positive history of FBTCS," "High frequency of previous FBTCS," "Velocity of AED load reduction," and "AED load at first seizure" (absolute and relative to VEM start) were significantly associated with the occurrence of FBTCS during VEM in both groups of patients (Table S2), whereas the other predictors were not (Table S3).

The reliable predictors include non-modifiable and modifiable factors. By comparing the predictive power of the reliable predictors using ROC analyses, "Relative AED load at first seizure" emerged as the best modifiable predictor (Table 1, Figure S2).

**TABLE 1** Receiver-operating characteristic (ROC): accuracy of reliable predictors for FBTCS during VEM[a]

| | N | AUC | *P* | 95% CI | |
|---|---|---|---|---|---|
| Non-modifiable predictors of FBTCS during VEM | | | | | |
| Positive history of FBTCS[b] | | | | | |
| Group 1 (2014/15) | 182 | 0.63 | .004 | 0.55 | 0.72 |
| Group 2 (2004/05) | 200 | 0.63 | .005 | 0.55 | 0.71 |
| High frequency of previous FBTCS[c] | | | | | |
| Group 1 (2014/15) | 139 | 0.79 | ≤.001 | 0.69 | 0.88 |
| Group 2 (2004/05) | 144 | 0.65 | .006 | 0.54 | 0.76 |
| Modifiable factors of FBTCS during VEM | | | | | |
| Velocity of AED load reduction | | | | | |
| Group 1 (2014/15) | 188 | 0.67 | ≤.001 | 0.59 | 0.75 |
| Group 2 (2004/05) | 203 | 0.69 | ≤.001 | 0.62 | 0.76 |
| Absolute AED load at first seizure | | | | | |
| Group 1 (2014/15) | 188 | 0.78 | ≤.001 | 0.72 | 0.85 |
| Group 2 (2004/05) | 203 | 0.72 | ≤.001 | 0.65 | 0.79 |
| Relative AED load at first seizure | | | | | |
| Group 1 (2014/15) | 188 | 0.78 | ≤.001 | 0.71 | 0.85 |
| Group 2 (2004/05) | 203 | 0.79 | ≤.001 | 0.73 | 0.85 |
| Null hypothesis | | 0.50 | | | |

[a]The null hypothesis describes a predictor at chance level.

[b]Only patients with data regarding history of FBTCS prior to VEM.

[c]Only patients with data regarding frequency of FBTCS prior to VEM.

## 3.3 | Predictors of FBTCS during VEM: Logistic regressions

To further evaluate the impact of the aforementioned modifiable factors, the association between occurrence of FBTCS during VEM and extent (given in steps of 10%) as well as velocity (given in steps of 10% per day) of AED load reduction were stratified according to the history and frequency of FBTCS prior to VEM, using hierarchical logistic regression analyses for three different scenarios (Tables 2–4). The chosen scenarios are common in everyday practice, where the clinician is challenged to define an AED tapering regimen based on the anamnestic information given by the patient.

In Scenario 1 (Table 2), history and frequency of FBTCS prior to VEM are neglected, and only modifiable predictors ("AED load reduction" and "Velocity of reduction") are accounted for. Taken individually, both of these factors are significantly predicting the occurrence of FBTCS (see $\chi^2$ and $R_N^2$ in models 1.1.1 and 1.1.2). Here, exp ($\beta$) indicates the multiplicative factor by which the odds of the dependent variable $P$("Occurrence of FBTCS") change when the respective predictor value changes by one unit (AED load reduction of 10%, velocity of reduction of 10% per day), that is, the odds ratio. It is important to note that the two modifiable predictors ("AED load reduction" and "Velocity of reduction") are significantly correlated with each other (Group 1: $r$ = .79***, Group 2: $r$ = .64***). Therefore, we also calculated a combined model (Model 1.2), where both predictors are included together. In comparison to "Velocity of AED load reduction" alone, the addition of "AED load reduction" significantly improved the predictive strength (Model 1.2 vs Model 1.1.1), whereas the combined model did not increase the predictive strength compared to "AED load reduction" alone (Model 1.2 vs Model 1.1.2). This finding suggests that "AED load reduction" is a much stronger predictor than "Velocity of reduction," of which the influence in the combined analysis is no longer significant. In the combined analysis (Model 1.2), the odds ratio, exp ($\beta$), for every 10% reduction per day is calculated at 0.99 in Group 2, indicating no meaningful influence of "Velocity of reduction" on FBTCS occurrence at all. In Group 1, the estimation is clearly below 1.00, exp ($\beta$) = 0.58, suggesting even a negative influence on FBTCS occurrence, although not a significant one. Taken together, one can conclude that "AED load reduction" is a better predictor for FBTCS than "Velocity of reduction."

In Scenario 2, the same analyses were performed after inclusion of the information on history of FBTCS as a non-modifiable factor (Table 3). In Group 1, a positive history of FBTCS (Model 2.1) already significantly increases the odds for FBTCS by a factor of exp ($\beta$) = 8.05 (odds ratio [OR]), corresponding to a relative risk (RR) of 5.47. Similarly, this holds also true for Group 2 (OR = 5.41, RR = 3.82). However, by adding the information on AED load reduction,

**TABLE 2** Scenario 1. Logistic regression without information on history or frequency of FBTCS

| Predictors | Group 1 (2014/15) N = 188 $\chi^2$ (df) | $R_N^2$ | exp ($\beta$) [95% CI] ≙ Odds ratio (OR) | Group 2 (2004/05) N = 203 $\chi^2$ (df) | $R_N^2$ | exp ($\beta$) [95% CI] ≙ Odds Ratio (OR) |
|---|---|---|---|---|---|---|
| Model 1.1.1 | | | | | | |
| Constant | 14.84 (1)*** | 0.11 | 0.16*** | 13.88 (1)*** | 0.09 | 0.22*** |
| Velocity of reduction | | | 2.46 [1.52, 3.99]*** | | | 1.63 [1.22, 2.18]*** |
| Model 1.1.2 | | | | | | |
| Constant | 42.04 (1)*** | 0.29 | 0.07*** | 43.09 (1)*** | 0.27 | 0.09*** |
| AED load reduction | | | 1.38 [1.24, 1.55]*** | | | 1.36 [1.23, 1.51*** |
| Model 1.2 | | | | | | |
| Constant | 43.71 (2)*** | 0.30 | 0.08*** | 43.09 (2)*** | 0.27 | 0.09 |
| Velocity of reduction | | | 0.58 [0.25, 1.35] ns | | | 0.99 [0.73, 1.36] ns |
| AED load reduction | | | 1.48 [1.26, 1.74]*** | | | 1.36 [1.21, 1.54]*** |
| Model comparisons | 1.2 vs 1.1.1 | | 1.2 vs 1.1.2 | 1.2 vs 1.1.1 | | 1.2 vs 1.1.2 |
| $\chi^2$ (df) | 28.87 (1)*** | | 1.67 (1) ns | 29.22 (1)*** | | 0.00 (1), ns |
| $\Delta R_N^2$ | 0.19 | | 0.01 | 0.18 | | 0.00 |

*Note:* $R_N^2$ = Nagelkerke (pseudo-) $R^2$.
AED load reduction [10% reduction of PDD/DDD].
Velocity of reduction [10% reduction of (PDD/DDD)/d].
***$P \leq .001$; ns = not significant.

**TABLE 3** Scenario 2. Logistic regression including information on history of FBTCS

| Predictors | Group 1 (2014/15) N = 182 $\chi^2$ (df) | $R_N^2$ | exp ($\beta$) [95%CI] ≙ Odds Ratio (OR) | Group 2 (2004/05) N = 200 $\chi^2$ (df) | $R_N^2$ | exp ($\beta$) [95%CI] ≙ Odds Ratio (OR) |
|---|---|---|---|---|---|---|
| Model 2.1 | | | | | | |
| Constant | 17.73 (1)*** | 0.13 | 0.07*** | 15.54 (1) *** | 0.11 | 0.10*** |
| History of FBTCS | | | 8.05 [2.37, 27.30]*** | | | 5.41 [2.03, 14.43]*** |
| Model 2.2.1 | | | | | | |
| Constant | 30.78 (2)*** | 0.22 | 0.03*** | 28.77 (2)*** | 0.19 | 0.05*** |
| History of FBTCS | | | 8.31 [2.39, 28.94]*** | | | 6.01 [2.08, 17.38]*** |
| Velocity of reduction | | | 2.47 [1.48, 4.15]*** | | | 1.61 [1.20, 2.15]** |
| Model 2.2.2 | | | | | | |
| Constant | 54.76 (2)*** | 0.37 | 0.01*** | 53.33 (2)*** | 0.33 | 0.02*** |
| History of FBTCS | | | 8.51 [2.31, 31.35]** | | | 5.16 [1.79, 14.92]** |
| AED load reduction | | | 1.38 [1.23, 1.56]*** | | | 1.36 [1.22, 1.51]*** |
| Model 2.3 | | | | | | |
| Constant | 55.71 (3)*** | 0.38 | 0.01*** | 53.43 (3)*** | 0.34 | 0.02*** |
| History of FBTCS | | | 8.18 [2.22, 30.23]** | | | 5.25 [1.80, 15.27]** |
| Velocity of reduction | | | 0.66 [0.29, 1.55] ns | | | 1.05 [0.77, 1.44] ns |
| AED load reduction | | | 1.46 [1.24, 1.72]*** | | | 1.35 [1.19, 1.52]*** |

| Model comparisons | 2.2.1 vs 2.1 | 2.2.2. vs 2.1 | 2.3 vs 2.2.1 | 2.3 vs 2.2.2 | 2.2.1 vs 2.1 | 2.2.2. vs 2.1 | 2.3 vs 2.2.1 | 2.3 vs 2.2.2 |
|---|---|---|---|---|---|---|---|---|
| $\chi^2$ (df) | 13.05 (1)*** | 37.03 (1)*** | 24.93 (1)*** | 0.95 (1) ns | 13.23 (1)*** | 37.78 (1)*** | 24.66 (1)*** | 0.10 (1) ns |
| $\Delta R_N^2$ | 0.09 | 0.24 | 0.15 | 0.01 | 0.08 | 0.23 | 0.14 | 0.00 |

** $P \leq .01$; ***$P \leq .001$; ns = not significant.

**TABLE 4** Scenario 3. Logistic regression including information on frequency of previous FBTCS

| Predictors | Group 1 (2014/15) N = 94 $\chi^2$ (df) | $R_N^2$ | exp ($\beta$) [95%CI] ≙ Odds Ratio (OR) | Group 2 (2004/05) N = 93 $\chi^2$ (df) | $R_N^2$ | exp ($\beta$) [95%CI] ≙ Odds Ratio (OR) |
|---|---|---|---|---|---|---|
| Model 3.1 | | | | | | |
| Constant | 23.15 (1)*** | 0.30 | 0.12*** | 4.26 (1)* | 0.06 | 0.32*** |
| Frequency of previous FBTCS | | | 10.54 [3.55, 31.34]*** | | | 2.51 [1.04, 6.08]* |
| Model 3.2.1 | | | | | | |
| Constant | 29.81 (2)*** | 0.38 | 0.04*** | 8.98 (2)* | 0.13 | 0.16*** |
| Frequency of previous FBTCS | | | 11.06 [3.54, 34.59]*** | | | 2.43 [0.98, 6.04] ns |
| Velocity of reduction | | | 2.77 [1.22, 6.33]* | | | 1.67 [1.03, 2.68]* |
| Model 3.2.2 | | | | | | |
| Constant | 36.61 (2)*** | 0.45 | 0.02*** | 19.42 (2)*** | 0.26 | 0.06*** |
| Frequency of previous FBTCS | | | 11.38 [3.48, 37.19]*** | | | 3.22 [1.19, 8.70]* |
| AED load reduction | | | 1.33 [1.12, 1.57]*** | | | 1.32 [1.13, 1.54]*** |
| Model 3.3 | | | | | | |
| Constant | 36.61 (3)*** | 0.45 | 0.02*** | 19.54 (3)*** | 0.26 | 0.07*** |
| Frequency of previous FBTCS | | | 11.38 [3.48, 37.20]*** | | | 3.31 [1.20, 9.10]* |
| Velocity of reduction | | | 0.99 [0.30, 3.29] ns | | | 0.89 [0.47, 1.70] ns |
| AED load reduction | | | 1.33 [1.06, 1.66]* | | | 1.35 [1.11, 1.64]** |

| Model comparisons | 3.2.1 vs 3.1 | 3.2.2 vs 3.1 | 3.3 vs 3.2.1 | 3.3 vs 3.2.2 | 3.2.1 vs 3.1 | 3.2.2 vs 3.1 | 3.3 vs 3.2.1 | 3.3 vs 3.2.2 |
|---|---|---|---|---|---|---|---|---|
| $\chi^2$ (df) | 6.66 (1)* | 13.46 (1)*** | 6.80 (1)** | 0.00 (1) ns | 4.73 (1)* | 15.16 (1)*** | 10.56 (1)** | 0.12 (1) ns |
| $\Delta R_N^2$ | 0.07 | 0.14 | 0.07 | . 00 | 0.07 | 0.20 | 0.14 | 0.00 |

*$P \leq .05$; ** $P \leq .01$; ***$P \leq .001$; ns = not significant.

the predictive power for occurrence of FBTCS even significantly improves (Model 2.2.2 vs Model 2.1), demonstrating that the risk of FBTCS to occur during VEM is predicted by AED load reduction beyond the patients' history of FBTCS. Whereas "Velocity of reduction" is also significantly increasing the predictive quality over "History of FBTCS" (Model 2.2.1), in the combined analysis with "AED load reduction" (Model 2.3), again, its influence is no longer significant. Of the patients with a negative history of FBTCS, the fraction that developed FBTCS during VEM was 6.67% in Group 1 (3 of 45) and 9.43% in Group 2 (5 of 53), see Table S1. Logistic regressions revealed that also in these patients, "AED load reduction" was a significant predictor for FBTCS occurrence and excelled "Velocity of reduction" (Table 5).

The analysis was further refined in Scenario 3 for patients with a positive history of FBTCS by including "Frequency of previous FBTCS" into the model (Table 4). In this scenario, high frequency of previous FBTCS is associated with a significantly greater risk of FBTCS during VEM in both groups (Group 1: OR = 10.54, RR = 5.18; Group 2: OR = 2.51, RR = 1.84). Again, "AED load reduction" as well as "Velocity of reduction" increase the predictive quality of the model, but in the combined analysis (Model 3.3) only "AED load reduction" plays an important role while "Velocity of reduction" no longer does.

We also aimed at quantifying the AED load reductions, which facilitate occurrence of FBTCS. To that end, we calculated the specific values for "AED load reduction" at a 50% probability of FBTCS (and a corresponding 50% probability of an FwoBTCS), based on the estimations of the combined models in the three scenarios. Because "Velocity of reduction" was shown to be less important than the actual AED load reduction, the following numbers are based on the observed mean levels of velocity. According to the estimation of Model 1.2, the probability of an FBTCS in Group 1 amounts to 50% when the relative AED load is reduced to 24.45% of the initial AED load at a mean

**TABLE 5** Threshold values for AED load reductions

| Scenario | Relative AED load | | | |
|---|---|---|---|---|
| | Group 1 (2014/15) | Group 2 (2004/05) | Mean | ~ |
| 1: No information on prior FBTCS | 24.45% | 20.34% | 22.39% | 20% |
| 2: Positive history of FBTCS prior to VEM | 32.28% | 28.37% | 30.33% | 30% |
| 3: High frequency of FBTCS prior to VEM | 52.50% | 43.79% | 48.15% | 50% |

*Note:* The results provide the actual AED load in relation to the AED load at VEM start (relative AED load) at the point of reduction when the probability for FBTCS becomes equal to the probability of FwoBTCS (0.5 or 50%), stratified by positive history and high frequency of FBTCS prior to VEM. Velocity of AED load reduction was fixed at the respective group mean value. Results are based on the estimated logistic regression models (Tables 2–4).

velocity of reduction of 8.69% per day. The analysis of Group 2 yields similar results, that is, an AED load reduction to 20.34% is associated with a probability of 50% for an FBTCS to occur during VEM at a mean velocity of 12.15% per day. Respective calculations were also performed for Models 2.3 and 3.3, resulting in thresholds for AED load reduction that represent a probability of 50% for an FBTCS under defined circumstances of history and frequency of FBTCS (see Table 5; see also Table S4 for lower FBTCS probabilities). No meaningful AED load reduction thresholds could be assessed for patients with a known negative history of FBTCS or a positive history but low frequency of FBTCS prior to VEM, due to an insufficient number of these specific cases.

## 4 | DISCUSSION

### 4.1 | Key findings

In two different patient groups separated by a decade, the occurrence of FBTCS during VEM depended on the patient's history and frequency of FBTCS prior to VEM and was strongly influenced by the extent of AED reduction during VEM. Crucially, although the amount and the rate of AED load reduction both mattered, the amount of reduction was shown to be a better predictor, even when taking into account history and frequency of previous FBTCS. Our study suggests that the risk of potentially deleterious FBTCS in an EMU is associated with AED load reduction and underscores the need for prospectively tested tapering protocols.

### 4.2 | Limitations

Our retrospective clinical study comes with limitations. First, AED load reduction regimens were not standardized, but depended on the individual decisions of the treating physicians and might have been unsystematically influenced by the patients' anamnestic information on prior FBTCS. Second, tapering regimens might have been different for varying types of AEDs. Both aspects are important, as AEDs can significantly differ with respect to pharmacokinetics, mechanisms of action, and drug-drug interactions on the one hand and efficacy on control of FBTCS on the other hand.[14] Because polypharmacotherapies varied considerably between individual patients, the effects of specific AED properties could not be systematically addressed. Being aware of these significant weaknesses, however, we have selected and analyzed two patient groups separated by a decade, assuming that the proportion of AEDs with distinct properties is very different (as shown in Figure S1) and that the treating physicians were different. It is important to note that only those factors that were shown to correlate significantly with FBTCS occurrence during VEM in the two patient groups were considered as reliable. This approach appeared to us as a reasonable way of mitigate the effects of individual tapering regimens and AED properties. Therefore, we are confident that despite the above-mentioned limitations, our findings are solid and the conclusions clinically meaningful.

### 4.3 | Clinical implications

According to a recent survey, only about one-third of the responding EMUs had a written policy for AED withdrawal during VEM.[2] Knowledge of the specific impact of AED load reductions on complications during VEM is limited, and available data focus mainly on the occurrence of status epilepticus and seizure clusters.[2,15,16] FBTCS are, however, far more frequent than status epilepticus during VEM[3,6,16] and are significantly related to physical injuries[5,17] and sudden unexpected death in epilepsy (or SUDEP)[8]. Previous studies dealing with FBTCS during VEM included between 54 and 151 patients, with 18% to 57% of them having FBTCS during VEM.[3,18–23] The proportion of people with FBTCS in our study (2014/15: 28%; 2004/05: 29%) was largely within the range reported by other studies. In previous studies, complete withdrawal of AED was associated with a twofold increase in FBTCS in VEM[3] and occurred more frequently in patients with a positive history of FBTCS prior to VEM,[24] yet risk factors were mostly not analyzed in greater detail or not validated in larger patient groups. However, a recent study investigated the rate of FBTCS in a dichotomous relation to estimated therapeutic vs nontherapeutic drug levels based on the patient's drug with the longest half-life, without finding significant effects.[25]

The present study provides a detailed approach and implies certain levels of AED load reductions that are associated with an elevated risk of FBTCS during VEM, considering the patient's history and frequency of previous FBTCS. As a quantitative measure we calculated the AED load of each VEM day and the relationship between the AED load at the day of seizure onset and the total AED load at VEM start, which allowed us to group and compare all patient data and to detect general patterns, irrespective of specific AED combinations.[26–28] Without taking into account information on FBTCS history, a 50% risk of an FBTCS during VEM was associated with a reduction to ~20% of the initial AED load. Taking into account a positive history of FBTCS, a 50% risk of an FBTCS during VEM was associated with a reduction to ~30%, and with taking into account a high frequency of previous FBTCS, a 50% risk of an FBTCS during VEM was associated with a reduction to ~50% of the initial AED load (see Table 5). The velocity of AED reduction during VEM does not seem to contribute significantly to the risk of FBTCS, which is in line with previous studies.[3,21] However, it must be acknowledged that due to the retrospective study design, a more important role of the tapering velocity cannot be ruled out, particularly concerning extremely high or extremely low rates of reduction, and may depend on specific AEDs.

In conclusion, we believe that our study provides practical estimates of AED load reductions that are associated with an elevated risk of FBTCS during VEM. Prospective studies are, however, recommended to corroborate our findings and to further investigate AED load reduction regimens for given drugs that specifically balance the risk of FBTCS during VEM and the length of the stay in an EMU.

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## CONFLICTS OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest. C.E.E. has served as a paid consultant for Desitin, Pfizer, and UCB Pharma. He was an employee of the Life and Brain Institute Bonn. R.S. has received fees as speaker or consultant from Bial, Desitin, Eisai, LivaNova, Novartis, and UCB Pharma. M.C.P. and M.S. have no conflicts of interest to disclose. 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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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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