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ORIGINAL COMMUNICATION

Seizure precipitants in a community-based epilepsy cohort

Merel Wassenaar · Dorothée G. A. Kasteleijn-Nolst Trenité · Gerrit-Jan de Haan · Johannes A. Carpay · Frans S. S. Leijten

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Abstract Epileptic seizures can be provoked by several factors. Better understanding of these factors may improve a patient's sense of control and could reduce seizures. In daily practice, the recognition of seizure precipitants relies heavily on clinical or video-EEG evidence, which can be difficult to obtain. Studies of seizure provocation are largely based on selected hospital-based patient populations, which may lead to biased occurrence estimates. Self-reported seizure precipitants are rarely studied, yet are necessary to understand the experiences of patients and improve epilepsy management. We performed a cross-sectional community-based study of 248 epilepsy patients, selected by pharmacy records of anti-epileptic drug use. Self-reported seizure precipitants and potential associated characteristics were assessed using questionnaires. Almost half of all patients (47 %) reported one or more seizure precipitants, of which stress, sleep deprivation, and flickering lights were the most common. In this community-based setting, light-provoked seizures were especially frequent compared to the literature. Idiopathic generalized epilepsy (IGE), a lower age at seizure onset, and having auras or prodromes were found to be important independent prognostic factors associated with provoked seizures. IGE and a younger age at seizure onset have been linked to provoked seizures in earlier reports. The finding of auras or prodromes as a prognostic factor was unexpected, though case reports have described provoked seizures in patients having auras. Assessment of these factors may facilitate the early recognition of seizure precipitants in daily clinical practice. This is important for the optimization of epilepsy management for a large group of patients, as provoked seizures are expected to occur frequently.

Keywords Epilepsy · Seizure precipitants · Provoked-seizures · Community-based

On behalf of the OPPEC study group.

Members of this group are listed in the Appendix section.

M. Wassenaar (✉) · F. S. S. Leijten
Department of Neurology and Neurosurgery, Clinical Neurophysiology HP: C03.229, Brain Center Rudolf Magnus, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands
e-mail: mwassenaar@sein.nl

M. Wassenaar · G.-J. de Haan
SEIN-Epilepsy Institute in the Netherlands Foundation, Heemstede, The Netherlands

D. G. A. Kasteleijn-Nolst Trenité
Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands

D. G. A. Kasteleijn-Nolst Trenité
Department of Neuroscience, University Sapienza, Rome, Italy

J. A. Carpay
Department of Neurology, Tergooi hospitals, Blaricum, The Netherlands

J. A. Carpay
Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

Introduction

Epileptic seizures can be provoked by external and internal factors [1, 2]. The prevalence of provoked seizures ranges from 29 to 92 % [2–13]. Internal precipitants such as stress or fatigue are well-known to increase seizure frequency [2, 3, 5, 8–11], and may also contribute to the occurrence of

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more specific reflex seizures [1]. These are seizures that frequently occur upon a specific sensory stimulus. Of these, clinical photosensitivity provoked by flickering light or flashing light patterns is the most common. Reflex seizures can be diagnosed clinically when a stimulus is presented, and confirmed by EEGs showing at least a 50 % increase in epileptiform discharges upon the provocative stimulus [1]. Failure to demonstrate the reflex mechanism does not rule out its existence. In many cases, enhancing factors such as stress or fatigue may be needed, [1] or it may take a longer stimulus presentation or more extensive evaluation before a relation is detected, as in reading or musicogenic epilepsy [14]. However, extensive evaluation, even by standardized procedures such as those developed for photosensitivity, are not consistently applied across different EEG laboratories [15]. For other, non-reflex provoked seizures, clinical evidence is even harder to obtain. Only a few cases have been reported; e.g., a case of emotional stress-induced epilepsy proven by EEG [16].

Recognition of provoked seizures for many physicians seems to rely on evidence from video EEG. This may cause an underestimation of its occurrence as, in practice, many more patients report specific circumstances that act as seizure triggers than can be investigated with video-EEG or any laboratory setting. Information on seizure precipitants requires extensive history-taking. Probably as a result, studies on provoked seizures performed in an unselected (non-clinic-based) patient population have been scarce [1, 8, 9].

For most seizure precipitants, little is known about associated characteristics such as predominant epilepsy type, age or gender [9]. Photosensitivity is mostly seen in childhood and adolescence and has been described predominantly in patients with idiopathic generalized epilepsies (IGEs), such as juvenile myoclonic epilepsy, juvenile or childhood absence epilepsy, and catastrophic epilepsy syndromes [17]. However, light-provoked seizures have also been reported in adult epilepsy patients [18, 19] and in patients with focal brain abnormalities, and can thus occur in any type of epilepsy [1, 19]. Knowledge of characteristics of patients experiencing provoked seizures may facilitate recognition of seizure precipitants. This could support epilepsy management by offering personalized measures to avoid these stimuli or to adapt lifestyle, providing patients with a better sense of control over their seizures [9] and contributing to seizure reduction [1, 6, 10].

The present study assessed the self-reported occurrence of internal and external seizure precipitants and their associated characteristics in a Dutch community-based cohort of adolescent and adult epilepsy patients. We also assessed which factors are independently prognostic for the occurrence of provoked seizures.

Methods

Population and setting

In 2010, we performed a cross-sectional community-based study of epilepsy characteristics and treatment outcomes in an outpatient population-based setting, approved by the local medical ethics committee. Patients were selected electronically from 30 public pharmacies in the (sub)urban area 'het Gooi-Utrecht' in the central part of the Netherlands. Epilepsy patients of at least 12 years of age with two or more anti-epileptic drug (AED) prescriptions in the last 2 years were identified by pharmacy dispensing records. Eligible patients were invited by regular mail to participate and received study information, an informed-consent form to be signed for inclusion, and a short questionnaire to confirm a diagnosis of epilepsy. Patients using AEDs for reasons other than epilepsy, such as pain, migraine, or depression, were excluded.

Data collection

We obtained demographic data (age, gender) as well as complete medication history, i.e., amount and type of both AEDs and co-medication including date, prescriber and dosage regimen covering at least the last 2 years, from the pharmacy records of included patients. After informed consent, patients received a questionnaire about epilepsy characteristics (seizure precipitants, epilepsy- and seizure-type, frequency, acceptability, a family history of epilepsy, auras or prodromes (premonitory symptoms), febrile seizures, and comorbidity) and treatment outcomes (seizure control in the previous 2 years, quality of life, and adverse events). Patients were asked if they experienced factors or circumstances that they considered to be commonly precipitating their seizures. If the answer was affirmative they were asked to indicate the type of precipitant from a list of potential seizure precipitants. The examples given were: stress, fatigue or sleep deprivation, fever, menses, alcohol use, sounds, flickering lights resulting from sunlight, disco-light, TV or videogames, or other factors that they could clarify by free text. With informed consent, full medical history data including a diagnosis, seizure semiology, EEG, and MRI results, as well as those from ancillary investigations (if applicable), were retrieved from epilepsy care providers (epileptologist, neurologist, or general practitioner). Data from both the questionnaire and medical history were discussed in clinical expert consensus meetings with four epileptologists. The available information was reviewed to be certain about a diagnosis of epilepsy and to classify the type of epilepsy according to the 1989 ILAE classification into localization-related, generalized, unclassified, and underlying etiology (symptomatic/cryptogenic

or idiopathic). A definite epilepsy classification was made if at least 75 % consensus was achieved.

Data analysis

Differences in demography, epilepsy, and treatment characteristics between patients with and without seizure precipitants were compared using one-way analysis of variance (ANOVA) or χ^2 tests. Multivariable logistic regression modeling with backward selection (P value <0.10) was used to assess the potential prognostic factors (age, age at onset, gender, epilepsy type, seizure control, seizure type, frequency and acceptability, febrile seizures, having auras or prodromes, a family history of epilepsy, comorbidity, adverse events, quality of life, co-medication, and number of current AEDs) associated with provoked seizures. They were presented with their odds ratios, 95 % confidence interval and p-values. Missing values were imputed by multiple imputation techniques to prevent biased estimates of results [20]. All statistical analyses were performed using IBM SPSS statistics for windows, version 20.0 (Armonk, NY: IBM Corp).

Results

Table 1 presents baseline characteristics of the 248 patients included. A total of 117 patients (47.2 %) reported at least one factor that could provoke their seizures. The majority (76.9 %) of these patients reported two or more seizure precipitants, with a maximum of six precipitants. Stress, sleep deprivation (fatigue), and flickering lights (sunlight, disco light, TV or videogames) were the most commonly reported seizure precipitants in 33.5, 25.0, and 17.3 % respectively. Seizures provoked by alcohol were reported in 6.9 %, sounds, fever, and menstruation in 5.2, 4.0, and 3.2 %, respectively, and 17.3 % reported an unclassified seizure precipitant such as pain, physical exercises, caffeine use, heat, or cold.

Table 1 Baseline characteristics for the total population and differences between patients with and without provoked seizures

	Total population ($n = 248$)	Provoked seizures ($n = 117$)	Seizures non-provoked ($n = 131$)	P value
Age (years), mean (sd)	52.1 (17.6)	47.2 (16.2)	56.4 (17.8)	<0.001
Age at onset (years), mean (sd)	31.5 (21.6)	22.7 (16.0)	39.5 (23.1)	<0.001
Male gender	54.4 %	47.0 %	61.1 %	0.027
Localization-related (symptomatic/cryptogenic) epilepsy	46.8 %	37.6 %	54.9 %	
Generalized (idiopathic) epilepsy	12.5 %	21.4 %	4.6 %	<0.001
Unclassified epilepsy	40.7 %	41.0 %	40.5 %	0.154
Auras or prodromes	46.0 %	63.2 %	30.5 %	<0.001
Epigastric aura		14.5 %	6.1%	
Sudden fear		7.7 %	2.3%	
Déjà vu		10.3 %	2.3%	
Tenuous sensation		22.2 %	13.7%	
Image or sound		7.7 %	2.3%	
Headache		6.0 %	2.3%	
Dizziness		13.7 %	9.2%	
Other (unclassified)		21.4 %	7.6 %	
Quality of Life (QOLIE-31), mean (sd)	72.0 (16.0)	70.5 (16.2)	73.3 (16.3)	0.189
Number of current AEDs, mean (sd)	1.17 (0.6)	1.15 (0.6)	1.19 (0.6)	0.636
Co-medication	77.4 %	76.1 %	78.6 %	0.631
Seizure control (no seizures in last 2 years)	54.4 %	51.3 %	57.3 %	0.346
>1 seizure per week (last year)	4.9 %	3.4 %	6.3 %	0.376
Generalized (sec.) seizures (TC)	72.6 %	77.8 %	67.9 %	0.084
History of febrile seizures	7.7 %	11.1 %	4.6 %	0.061
Family history of epilepsy	30.2 %	31.6 %	29.0 %	0.654
Acceptability of uncontrolled seizures	54.2 %	57.3 %	51.5 %	0.514
Adverse events	82.7 %	85.5 %	80.2 %	0.271
Comorbidity	44.0 %	40.2 %	47.3 %	0.257

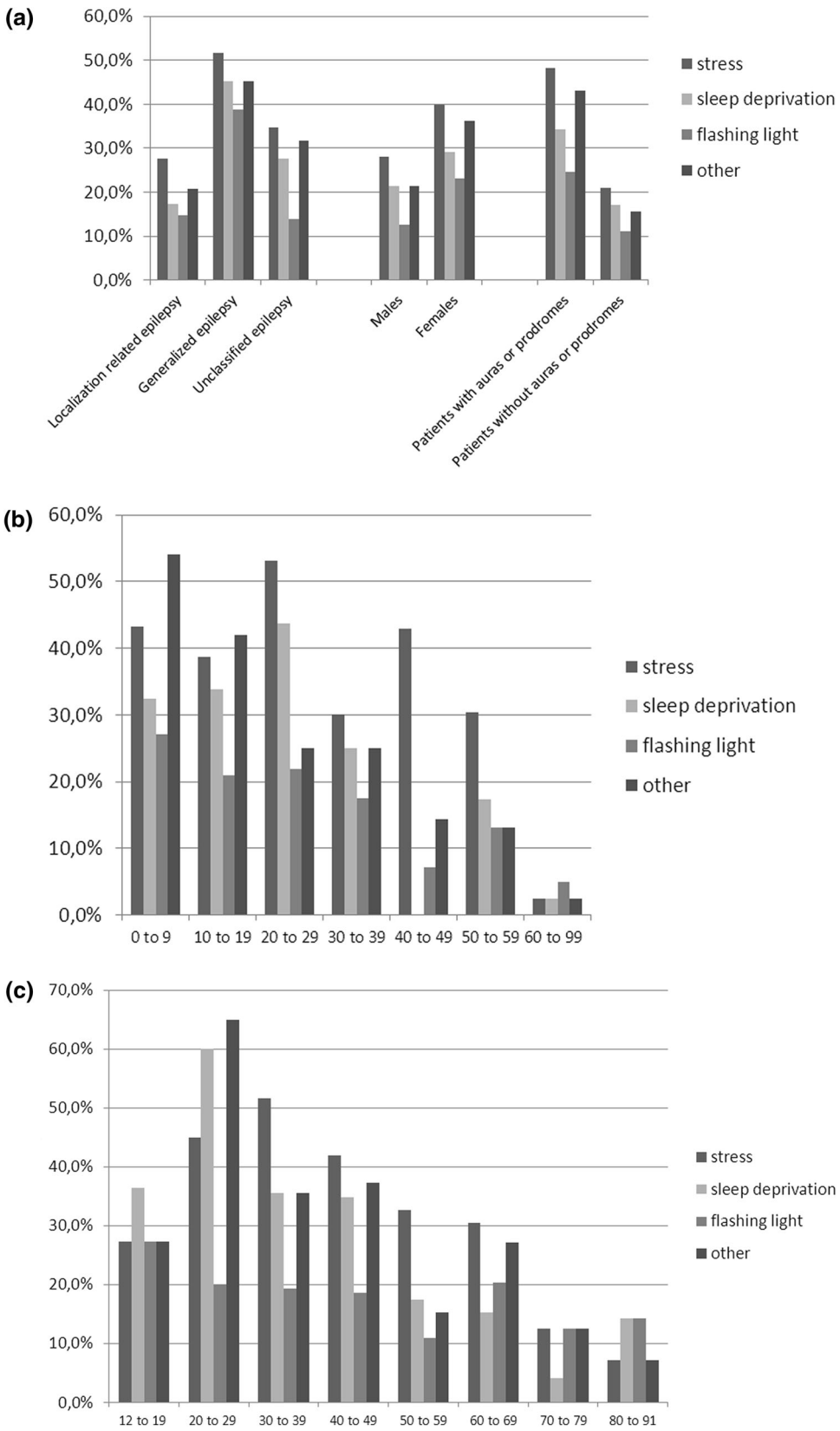

Fig. 1 **a** Percentages of reported (types of) provoked seizures per type of epilepsy, gender, and having auras or prodromes. **b** Percentages of reported (types of) provoked seizures per age at seizure onset. **c** Percentages of reported (types of) provoked seizures per age

Table 2 Prognostic factors associated with provoked seizures

	OR	95 % CI	*P* value
Age at onset	0.967	0.952–0.982	<0.001
Auras or prodromes	4.043	2.247–7.274	<0.001
Localization related epilepsy (ref)	–	–	–
Idiopathic generalized epilepsy	4.212	1.434–12.371	0.009
Unknown epilepsy type	1.102	0.585–2.075	0.763

Patients without seizure control were more likely to report provoked seizures (50.4 %) than patients with well-controlled seizures (44.4 %), especially stress and light-provoked seizures, though this was not statistically significant. Patients with IGE, a lower age at seizure onset, patients having auras or prodromes (tenuous sensation, epigastric aura, déjà vu, sudden-fear, image or sound, headache or dizziness) as well as female patients and those of a younger age were more likely to report provoked seizures. Differences in baseline characteristics between patients with and without provoked seizures are given in Table 1. Figure 1 presents proportions of the different types of precipitants (stress, sleep deprivation, flickering lights, and other) for those characteristics that have been found to be associated with reporting provoked seizures; i.e., type of epilepsy, gender, and having auras or prodromes (Fig. 1a), age (Fig. 1b), and age at seizure onset (Fig. 1c).

Multivariable logistic analysis found that a younger age at seizure onset, having IGE, and having auras or prodromes were independent prognostic factors of the occurrence of provoked seizures (Table 2). There was no prognostic role for age, gender, a (secondary) generalized seizure type, seizure-control, acceptability, or frequency. Also, a family history of epilepsy, a history of febrile seizures, comorbidity, the number of current AEDs, the use of co-medication, adverse events, or quality of life were not found to be independently prognostic for provoked seizures.

Discussion

Principal findings

In our study, 47 % of patients reported provoked seizures. This is within the range (29–92 %) found in other studies [2–12]. As we performed our study in an adolescent and adult population from a community-based patient group, the prevalence of provoked seizures was remarkably high. Provoked seizures, especially photosensitivity, have been found associated to younger age [1, 9, 17]. Yet, a clear relation between age and the occurrence of provoked seizures has not been consistently found [3, 5]. Most earlier studies were not purely population-based and reported higher percentages [2–5, 7, 10–12]. This is probably due to the fact that in a clinical (non-community) setting patients are expected to be more therapy-resistant and more likely to be aware of precipitating factors. These patients may be more thoroughly interviewed and informed about seizure precipitants, resulting in higher numbers of reported precipitating factors. Patients with more disabling seizures may also be more likely to seek causes related to their seizures to understand why their seizures started in the first place, in an effort to predict the occurrence of their seizures [21, 22]. Our study, indeed, demonstrated that patients without seizure control reported slightly more provoked seizures (50.4 %) than patients with well-controlled seizures (44.4 %), though this did not reach statistical significance.

Occurrence of seizure precipitants

As in previous studies, stress and fatigue were the most reported seizure precipitants [2, 3, 5, 8–11, 22]. Cases of stress-induced seizures have been described [16], and both animal as well as psychopharmacologic and behavioral intervention studies have suggested a link between stress and seizure frequency, though its causal role remains unclear [22–24].

A total of 17 % of patients reported seizures provoked by flickering light, which is higher than the 5–7 % of epilepsy patients found to be photosensitive in earlier studies [1, 8, 25]. This discrepancy is likely due to the use of questionnaire data instead of EEG-confirmed photosensitivity. Seizures provoked by flickering lights were, in line with earlier reports on photosensitivity, more frequently reported by female patients [1, 17, 19, 26]. However, studies that focused on provoked seizures in general did not find an association between light-provoked seizures and female gender, probably due to the small numbers of light-provoked seizures in these studies [2, 3, 5, 7, 9].

Characteristics associated with provoked seizures

In multivariable analysis, three factors (IGE, a younger age at seizure onset, and auras or prodromes) were found to be the most important independent prognostic factors related to the presence of provoked seizures. Their assessment can be used to predict the likelihood of provoked seizures and aid in epilepsy management [8, 36]. Gender and a younger age per se were not found to be important prognostic factors of (light-) provoked seizures.

Light, as well as other precipitants were more frequently reported by patients with a younger age at seizure onset and having IGE. This is in line with earlier reports on

photosensitivity [17, 19, 26]. Nakken et al. also found an association of IGE with other types of seizure precipitants (sleep deprivation and fatigue) [8]. Though the relation between the type of epilepsy and provoked seizures has not been extensively been studied, it is certainly not limited to generalized epilepsies, as provoked seizures have also been found in other epilepsy types, such as temporal lobe epilepsy (TLE) [5, 7]. In our study, provoked seizures were more frequently reported by patients with auras or prodromes, independent of its type. This was remarkable and has only been found in one other study [2]. This study was performed in a somewhat younger population (mean age 35.9 years) attending an epilepsy clinic. In their study, 85 % of patients with auras reported provoked seizures, which was slightly higher than our finding of 63 %. In contrast to our study, they found no single precipitant to be reported more significantly by patients with auras, which is probably due to the high number of patients with auras. No further details on types of auras were given, but due to the high percentage this is likely to include prodromes as well. Most studies on seizure precipitants did not consider a potential association with auras or prodromes, and consequently did not find one. Auras may have been neglected because auras suggest partial seizures [27], and provoked seizures are generally associated with IGE. Spatt et al. [2] considered their finding unlikely and argued that it may be a result of interpretation difficulties. It may be difficult for patients to discern early seizure symptoms (auras) or prodromes from seizure precipitants [8]. In addition, patients having simple-partial seizures (auras) only without loss of consciousness may be more capable of remembering and thus reporting seizure precipitants, leading to some overrepresentation.

Nevertheless, case reports have described patients with localization-related epilepsies like TLE with auras and photosensitivity [28, 29]. A parallel can perhaps be drawn with migraine attacks in which precipitating factors are well-known. Both epilepsy and migraine are related to intermittent changes in brain excitability and often co-occur, and there is growing evidence of a genetic and clinical overlap between both [30–33]. Especially occipital-lobe epilepsy has several similarities with migraine, such as visual aura, positive and negative ictal signs, and autonomic disturbances (pallor and vomiting) [30, 34]. In patients with migraine with aura, a clear association was found with photosensitivity [35]. In a similar way, auras and photosensitivity may thus be linked in epilepsy, although the underlying mechanisms are not yet fully understood [30].

Strengths and weaknesses

This is one of the first studies of self-reported seizure precipitants in a community-based, rather than a hospital-based, epilepsy population [8, 9]. A community-based setting is more representative of epilepsy cases in general. It also includes patients with well-controlled epilepsy who do not require specialized care and are frequently neglected in epilepsy research. A disadvantage, however, is that available clinical information is less detailed. To be able to correctly classify epilepsy, we used extensive clinical expert reviews of medical files and questionnaire data. Epilepsy classifications were made if at least 75 % consensus on the type of epilepsy was achieved based on the available information. This was obtained in about 60 %; in the other 40 % there was consensus about a diagnosis of epilepsy, but no definite classification was possible. These percentages are consistent with previous studies relying on the same type of data, although large differences between countries do exist [8].

Another potential limitation of our study is the use of self-reported data and the lack of confirmation of especially clinical photosensitivity by EEG data. Some patients may oversimplify the explanations for their seizures, as they tend to search for situations or factors that may cause their seizures [8], thus leading to biased results. Studying provoked seizures based on clinical or diagnostic evidence may, however, be biased as well. The nature of potential seizure precipitants is often subjective, and evidence such as EEG confirmation is often difficult to obtain, or even false-negative when circumstances are not reliably reproduced. The question of seizure precipitants may be neglected by physicians in, e.g., the elderly or patients with localization-related epilepsy presumed not to suffer from provoked seizures. Consequently, this type of research relying on self-reported data is necessary to understand the perceptions and experiences of epilepsy patients [9], whose views should be taken seriously even in the absence of clinical or diagnostic evidence.

Conclusion

A large percentage of epilepsy patients report that their seizures can be provoked by one or more precipitating factors, of which stress, sleep deprivation, and flickering lights are the most important. Seizure precipitants are not limited to younger patients and those with generalized epilepsies. A number of readily available clinical characteristics such as age at onset, epilepsy type, and occurrence of auras or prodromes were found to be independent prognostic factors associated with the occurrence of provoked seizures and may aid in the early recognition of provoked seizures. Better recognition of patient-perceived provoked seizures is important, even though clinical or diagnostic evidence is not always available and causal relations are not always clear. This must be part of epilepsy

management in order to provide patients with information and with measures to avoid certain triggers, which may cause a better sense of control and may reduce seizure load.

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Conflicts of interest All authors declare no conflict of interests. A grant provided by the National Dutch Epilepsy Foundation was received for the conduct of the OPPEC study that forms part of the submitted work. All authors have no financial relationship with any organization that might have an interest in the submitted work or relationships or activities that could appear to have influenced the submitted work.

Ethical 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. The study has been approved by the local ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Appendix

The following are members of the OPPEC study group in alphabetical order: J A. Carpay (M.D., Ph.D.), A C.G. Egberts (Ph.D.), G.J. de Haan (M.D., Ph.D.), D.G. Kasteleijn-Nolst Trenité (M.D., Ph.D.), B.P. Koeleman (Ph.D.), F.S.S. Leijten (M.D., Ph.D.), P. van der Linden (Ph.D.), D. Lindhout (Ph.D.), K.G.M. Moons (Ph.D.), S.G. Uijl (Ph.D.), M. Wassenaar (M.Sc.), I. Wilting (Ph.D.) all residing in the Netherlands, and J.W. Sander (M.D., Ph.D.) (United Kingdom). All members of the OPPEC study group were involved in the design of the study. MW was responsible for the design/conceptualization of the study, the collection, analysis, and interpretation of the data and for drafting the manuscript. DK, GdH, JC, and FL were responsible for the design/conceptualization of the study, revising the manuscript for intellectual content and for final approval of the version to be published. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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