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Yield and risk associated with prolonged presurgical video-EEG monitoring: a systematic review

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ABSTRACT

Objective. Presurgical long-term video-EEG monitoring (LT-VEEG) is an important part of the presurgical evaluation in patients with focal epilepsy. Multiple seizures need to be recorded, often in limited time and with the need to taper anti-seizure medication (ASM). The aim of this study was to systematically study the yield – in terms of success – and risks associated with presurgical LT-VEEG, and to identify all previously reported contributing variables.

Methods. A systematic review of the databases of PubMed Medline, Embase, Cochrane Central, and the Cochrane Database of Systematic Reviews were searched following the Preferred Reporting Items for Systematic Reviews (PRISMA) guideline. Publications about presurgical LT-VEEG reporting on variables contributing to yield and risk were included. Study characteristics of all included studies were extracted following a standardized template. Within these articles, studies presenting multivariable analyses of factors contributing to the risk of adverse events or the success of LT-VEEG were identified.

Results. We found 36 articles reporting on LT-VEEG, including 4,703 presurgical patients, both children and adults. Presurgical LT-VEEG monitoring led to an average yield of 85%. Adverse events occurred with an averaged total event rate of 17%, but the type of included events was variable among studies. Factors reported to independently contribute to successful LT-VEEG were: baseline seizure frequency, a shorter interval from the most recent seizure, extra-temporal lobe epilepsy, and no requirement for ASM reduction. Factors independently contributing to the occurrence of adverse events were: ASM tapering, a history of status epilepticus, a history of focal to bilateral tonic-clonic seizures, psychiatric comorbidity, and ASM taper rate.

Significance. This study reveals that the data on factors contributing to yield and risk of adverse events is significant and variable, and often reported with inadequate statistics. Future research is warranted to develop guidelines for ASM withdrawal during presurgical video-EEG monitoring, taking predefined factors for success and risks of adverse events into account.

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Up to two-thirds of properly selected people with medically refractory focal epilepsy will be seizure-free (Engel Class 1 outcome), five years after epilepsy surgery [1]. Presurgical long-term video-EEG (LT-VEEG) monitoring is an essential part of the mapping of the seizure onset zone. In lesional neocortical epilepsy, a lateralised and localised seizure pattern on ictal scalp EEG is associated with a favourable individual outcome [2]. The required number of seizures monitored to ensure a reliable assessment of seizure semiology and ictal onset EEG patterns varies, depending – among other factors – on the pre-test probability of unifocal epilepsy [3-5]. Presurgical LT-VEEG often involves controlled provocation of seizures, which increases its yield but not without risks. The most commonly used provocation method is anti-seizure medication (ASM) withdrawal [6], which may result in adverse events such as focal to bilateral tonic-clonic seizures (FBTCS), seizure clusters, or even status epilepticus [7]. Little is known about independent determinants of yield and risk of LT-VEEG. Despite many reports of in-house provocation models, no standardised or best practice recommendation is available.

To mitigate these risks and infer safe and successful presurgical LT-VEEG, we systematically reviewed the available evidence on variables that contribute to the success and adverse events of LT-VEEG.

Materials and methods

This systematic review followed a predefined protocol guided by the Preferred Reporting Items for Systematic Reviews (PRISMA).

Search strategy

We searched PubMed Medline, Embase, Cochrane Central, and the Cochrane Database of Systematic Reviews using terms related to presurgical LT-VEEG to find studies reporting variables that contribute to its success or risks (*supplementary table 1*). Long-term monitoring was interpreted as all monitoring over a day or longer. We included retrospective and prospective observational studies and randomised controlled trials. We also screened the reference list of the identified articles to identify studies that our search strategy may have missed. The last search was performed in December, 2021.

Study selection and eligibility criteria

Two reviewers (CvA and RvR) independently screened the titles and abstracts. In case of disagreement, the full text was discussed. Reports on fewer than 20 subjects were not deemed to be representative and were therefore excluded. We also excluded studies in languages other than English, German or Dutch. In case of duplicate studies with overlapping populations from the same centre, only the report deemed most contributing was included. Surveys and guidelines for presurgical video-EEG monitoring were also excluded.

Data extraction and data collection

One reviewer (RvR) extracted data using a standardised form. A second reviewer (CvA) checked random sets of extracted data. Study characteristics were also collected (*supplementary table 2*). Data were categorised into: (1) LT-VEEG logistical characteristics, such as mean length of stay, design of the epilepsy monitoring unit (EMU), and whether or not a nurse or technician was continuously present during the monitoring; (2) individual variables of age, gender, seizure frequency before admission, history of status epilepticus, seizure clustering, or FBTCS; (3) LT-VEEG variables of mean number of seizures recorded, yield, seizure onset localisation, and provocation methods used (including the presence or absence of a predefined withdrawal protocol). We used the definition of LT-VEEG "yield", as suggested in individual study reports. In general, LT-VEEG was considered successful when the clinical question was answered. If this was not explicitly reported, LT-VEEG was deemed successful when seizures or events were recorded. A standardised selection was made of the most common adverse events: non-habitual FBTCS or seizure clusters, status epilepticus, other events (for example, falls and postictal psychosis), and the total rate of adverse events. FBTCS were only scored as adverse events when they occurred for the first time or were highly unusual for that individual. Seizure clusters were defined as three or more seizures in either four hours or 24 hours, since these different definitions of seizure clusters have both been applied in previously published studies. Preferably, only non-habitual seizure clusters were scored as adverse events. However, for cases in which this was not explicitly mentioned by the authors of studies, all clusters were scored. Information on possible contributing variables for yield and adverse events associated with LT-VEEG was collected when such a variable was identified in at least one study as a significant determinant in multivariate analyses. When possible, we looked at the difference between children and adults. We used the Strengthening in the Reporting of Observational Studies in Epidemiology (STROBE) checklist to assess study quality.

Results

Study selection and study characteristics

We selected 36 reports from 2,679 identified articles (*supplementary figure 1*). These 36 reports included 13,603 individuals (1,351 children, a subset of 8,782 adults and children combined, and 3,470 adults). In total, 4,703 were monitored for presurgical purposes and 3,976 for other diagnostic purposes. In 4,924 individuals, the LT-VEEG indication was not explicitly reported (*table 1*). All collected variables are presented in *supplementary table 2*. Some studies reported their outcomes separately for the presurgical group, but not for all outcomes. The inclusion and exclusion criteria differed among the studies. Some studies excluded individuals when seizures were recorded, ASM was not used, or ASM withdrawal was not performed. It was not always clear whether individuals experienced habitual FBTCS or seizure clusters, or whether or not these were considered adverse events. Some studies investigated outcome from only a single event during (presurgical) VEEG, for example seizure clusters. The number of studies that included only surgical candidates was small. We pooled data from these studies with presurgical patient data extracted from mixed study cohorts to describe the yield of LT-VEEG and associated adverse event rates. To collect information on determinants of LT-VEEG yield and adverse events, we used all patient data from the 36 included studies – independent of whether the recording was for presurgical reasons or otherwise – as long as multivariate analysis techniques to identify independent predictors were used.

Yield of presurgical LT-VEEG

The yield of presurgical LT-VEEG was specifically addressed in nine studies with a total rate of success of 85% (n= 1,654/1,943) and a mean duration of LT-VEEG of 4.9 days (*table 1*). When looking specifically at children or adults, the success rate was respectively 80% (n= 237/295, four studies) and 71% (n= 97/136, two studies). Definitions of success among studies varied between only seizures recorded, seizures recorded that were sufficient to proceed with presurgical evaluation, and whether or not the referral question was answered. Some studies did not explicitly mention the yield or success rate but only noted the type and/or seizure frequency and whether any episode was recorded; these were categorized as not reported. In children, medication was less often tapered than in adults (40% and 68%, respectively) and the mean duration of LT-VEEG was shorter (four days versus 5.2 days).

▼Table 1. Characteristics of all included studies.

Author (year)	Study period	Total number of individuals	Presurgical LT-VEEG	Population and study design	Mean age (yrs)	Mean length of stay (days)	Mean number of seizures recorded	Habitual seizure frequency	Medication withdrawal (Yes/No) (%)	Yield of successful monitoring (all cases, %)	Yield of successful monitoring in presurgical cases only (%)
Babtain *et al.* (2021) [18]	2018-2021	104	NR	All ages (>13)	30	5 (pre-COVID) 3 (post-COVID)	4/6	Daily: 4(6%) / 4(10%) 2-4/month: 39 (63%) / 25(60%) 1x/3-6 months: 14 (23%) / 10 (24%) 1x/12-18 months: 4 (6%) /3 (7%)	Yes	81 (78%)	NR

▼Table 1. Characteristics of all included studies (*continued*).

Author (year)	Study period	Total number of individuals	Presurgical LT-VEEG	Population and study design	Mean age (yrs)	Mean length of stay (days)	Mean number of seizures recorded	Habitual seizure frequency	Medication withdrawal (Yes/No) (%)	Yield of successful monitoring (all cases, %)	Yield of successful monitoring in presurgical cases only (%)
Baheti, *et al.* (2011) [25]	1996-2009	148	87	Elderly (>45) Retrospective	51	2.9	3.2	NR	Yes 109 (74%)	95%	NR
Chen *et al.* (1995) [26]	1991-1992	226	24	Children Retrospective	NR	NR	NR	Daily: 183 (81.%) Weekly: 35 (15.5%) <Weekly: 8 (3.5%)	Yes 2 (8%)	80%	64%
Cox *et al.* (2020) [15]	2018-2019	1062	83	All ages Prospective	26	5 (presurgical)	NR	NR	Yes (presurgical) 73 (86%)	40%	75%
Craciun *et al.* (2017) [13]	2012-2016	976	NR	All ages Prospective	25	3.2	NR	NR	Yes 284 (29%)	62%	
Di Gennaro *et al.* (2012) [27]	2010	76	76	Adults Retrospective	33	6	3.5	NR	Yes 54 (71%)	93%	93%
Dobesberger *et al.* (2011) [28]	1999-2005	507	279	All ages Retrospective	36	5	4	NR	Yes	81%	NR
Duy *et al.* (2020) [8]	2016-2017	114	114	All ages Retrospective	33	6.3	5	NR	Yes	NR	NR
Fahoum *et al.* (2016) [20]	2011-2014	524	80	Adults Retrospective	36	7.2	9.3 (no ASM) 17.2 (AE)	NR	Yes 260 (50%)	79%	NR
Fung *et al.* (2018) [29]	2009-2011	69	69	Children Retrospective	12	5	6	<1/month: 11 (16%) <1/week: 22 (32%) >1/week: 36 (52%)	Yes 63 (91%)	NR	NR
Grau-Lopez *et al.* (2020) [14]	2007-2019	411	NR	Adults Retrospective	42	5.1	NR	NR	Yes	NR	NR

▼Table 1. Characteristics of all included studies (*continued*).

Author (year)	Study period	Total number of individuals	Presurgical LT-VEEG	Population and study design	Mean age (yrs)	Mean length of stay (days)	Mean number of seizures recorded	Habitual seizure frequency	Medication withdrawal (Yes/No) (%)	Yield of successful monitoring (all cases, %)	Yield of successful monitoring in presurgical cases only (%)
Griethuysen *et al.* (2018) [22]	2005-2011	276	174	All ages Retrospective	34	4	3	NR	Yes 182 (66%)	84%	NR
Guaranha *et al.* (2005) [30]	1988-2001	97	97	All ages Retrospective	30	3.3	7.3	NR	Yes 97 (100%)	NR	NR
Guld *et al.* (2017) [11]	2011-2013	79	79	All ages Retrospective	34	4.3	5.3	3.9/month	Yes 79 (100%)	NR	NR
Harini *et al.* (2013) [31]	2009-2011	95	95	Children Retrospective	12	5.5	6	<1/month: 22 (23%) <1/week: 18 (19%) >1/week: 55 (58%)	Yes 95 (100%)	NR	NR
Haut *et al.* (2002) [32]	1998-1999	91	91	Adults Prospective	33	NR	NR	NR	Yes 49 (54%)	NR	NR
Henning *et al.* (2014) [33]	2010-2011	60	60	Adults Prospective	34	3	3.4	0.4 / day	Yes 60 (100%)	43%	43%
Jonas *et al.* (2011) [34]	2007-2008	80	51	All ages Prospective	32	NR	NR	NR	Yes. presurgical 51 (100%)	NR	NR
Kasab *et al.* (2017) [35]	2012-2014	439	241	Adults Retrospective	NR	3.1	1.7/day	0.7/day	Yes	NR	NR
Keller *et al.* (2018) [36]	2014-2016	281	139	Children retrospective	10	2.6	NR	NR	Yes 108 (38%)	55%	NR
Kumar *et al.* (2018) [21]	2016-2017	140	123	All ages Randomized controlled trial	9.1 (rapid taper) 11.3 (slow taper)	4.7 (rapid taper) 6.6 (slow taper)	5.1 (rapid taper) 4.6 (slow taper)	9.4/month (rapid taper) 8.2/month (slow taper)	Yes (100%)	96% (rapid taper) 97% (slow taper)	NR

▼Table 1. Characteristics of all included studies (*continued*).

Author (year)	Study period	Total number of individuals	Presurgical LT-VEEG	Population and study design	Mean age (yrs)	Mean length of stay (days)	Mean number of seizures recorded	Habitual seizure frequency	Medication withdrawal (Yes/No) (%)	Yield of successful monitoring (all cases, %)	Yield of successful monitoring in presurgical cases only (%)
Lampe, *et al.* (2014) [10]	2010-2011	132	40	Adults Retrospective	37	4.4	NR	<1/week: 52 (42%) >1/week and <1/day: 47 (38%) >1/day: 24 (20%)	Yes	82%	NR
Ley, *et al.* (2014) [12]	2009-2012	175	119	All ages Retrospective	36	5.8	4	6/month	Yes 132 (75%)	100%*	NR
Lim, *et al.* (2020) [37]	2012-2016	137	137	All ages Retrospective	35	3	7	NR	Yes	80%	80%
Mann *et al.* (2021) [38]	2016-2019	178	88	Children	11	5.4	NR	Daily: 48 (27%) >1/week: 27 (15%) 1/week: 10 (5.5%) 1-3/month: 30 (17%) <1/month: 20 (11%)	NR	54%	84%
Moien-Afshari *et al.* (2009) [39]	2006-2008	50	20	Adults Prospective	36	4.4	5	12/month	Yes 49 (98%)	88%	NR
Noe *et al.* (2009) [40]	2005-2006	149	89	Adults Prospective	44	5.7	5.0	NR	Yes	73%	NR
Pensel *et al.* (2020) [9]	2004-2005 /2014-2015	391	391	Adults Retrospective	36	NR	NR	NR	Yes	NR	NR
Riquet *et al.* (2011) [23]	1999-2005	380	61	Children Retrospective	7	1.5	NR	Yes	Yes 114 (36%)	59%	69%

▼Table 1. Characteristics of all included studies (*continued*).

Author (year)	Study period	Total number of individuals	Presurgical LT-VEEG	Population and study design	Mean age (yrs)	Mean length of stay (days)	Mean number of seizures recorded	Habitual seizure frequency	Medication withdrawal (Yes/No) (%)	Yield of successful monitoring (all cases, %)	Yield of successful monitoring in presurgical cases only (%)
Rizvi *et al.* (2014) [41]	NR	158	52	All ages Prospective	37	4.5	9.1	8.0/month (presurgical)	Yes	90.5%	NR
Rose *et al.* (2003) [42]	2000	514	NR	Adults Retrospective	NR	NR	4.3	NR	Yes	NR	NR
Sauro *et al.* (2014) [43]	2008-2011	396	162	Adults Prospective	37	9.4	13.9	Yes	Yes 306 (79%)	79%	NR
Schulze-Bonhage *et al.* (2022) [17]	2005-2020	1922 (UKF) 2919 (KCL)	1335 (UKF)	All ages Retrospective	NR	5.2 (UKF, all) 5.9 (UKF, presurgical) 4.4 (KCL)	NR	NR	Yes (78.5%) (UKF)	73% (UKF) 42% (KCL)	1148/129288.9% (UKF)
Sun *et al.* (2015) [24]	2010-2013	122	122	Children Retrospective	10	4	NR	Yes	Yes 67 (55%)	87%	87%
Swick *et al.* (1996) [44]	1993-1994	36	36	NR Prospective	NR	7.4 temporal group 5.6 extra-temporal group	5.5 temporal group 10.4 extra-temporal group	Yes	Yes 22 (61%)	NR	NR
Yen *et al.* (2001) [45]	1995-1997	89	89	Adults Retrospective	31	6.4	4.8	NR	Yes 89 (100%)	NR	NR
Total		**13.603**	**4703**			**All: 4.9 Adults: 5.2 Children: 4.0**			**Adults: 68% (976/1434) Children: 40% (465/1173)**	**62%% (*n* = 6933/11.098)**	**85% (*n*= 1654/1943) Adults: 71% (*n*= 97/136) Children: 80% (*n*= 237/295)**

NR: not reported
*in 1-3 recordings.

Factors determining the odds of successful LT-VEEG

Eighteen studies investigated the determinants of LT-VEEG yield using univariate analysis and three using multivariate analysis. Nine factors (higher baseline frequency, shorter interval from the most recent seizure, no requirement for ASM reduction, extra-temporal lobe epilepsy, ASM withdrawn during monitoring, use of hyperventilation provocation, length of stay, presurgical recording and younger age at onset) were reported as being univariately associated with successful monitoring. In multivariate analyses, only five factors were independently associated with the chance of successful presurgical LT-VEEG; higher baseline seizure frequency, shorter interval from the most recent seizure, extra-temporal lobe epilepsy, ASM reduction and ASM reduction deemed unnecessary (*table 2*). The most frequently reported factor was baseline seizure frequency, associated with LT-VEEG success in nine of 11 studies based on univariate analyses and in both two studies that applied multivariable analysis.

All 36 studies reported ASM withdrawal as a seizure provocation method to be applied in most individuals during presurgical LT-VEEG. Most studies used a local protocol with individual adjustments based on specific clinical characteristics such as baseline frequency and history of adverse events (*e.g.* status epilepticus). ASM withdrawal was associated with success of LT-VEEG in four of 11 studies in univariate analyses, but only one confirmed this as an independent factor in multivariable analyses. Another study showed, using multivariable analysis, that when ASM withdrawal was not needed, this was independently related to successful monitoring. In this study, however, baseline seizure frequency – presumably strongly linked to the consideration that ASM withdrawal was not needed – was not included in the model.

Adverse events during presurgical LT-VEEG

Eleven studies, including data from 951 individuals, reported the proportion of surgical candidates with one or more adverse events (*table 3*), with a total adverse event rate of 17% (106 of 607 individuals). Comparison of adverse events in children and adults was not possible because of insufficient data. There was extensive variety in the type of events investigated and documented as "adverse" events (*supplementary figure 2*). Not all studies reported each adverse event separately; some only provided the total proportion of individuals with one or more event. Non-habitual FBTCS were reported in 5% of 473 individuals in six studies. Only one study explicitly reported the occurrence of non-habitual seizure clusters; most studies included all individuals with a seizure cluster without providing clarity on whether or not individuals with habitual clusters were excluded. Clusters, defined as three or more seizures in four hours, were reported in 15% (67/444) individuals in four studies. Clusters defined as three or more seizures in 24 hours were reported in 34% (178/525) individuals.

Factors determining the risk of adverse events

Fourteen studies investigated factors that correlated with the risk of adverse events using univariate analyses, and eight with multivariate analyses. In total, 21 factors (*supplementary figure 3*) were reported to be univariably associated with the adverse event rate. Based on multivariate analyses, 12 factors were independently associated: ASM tapering, a history of SE, history of FBTCs, psychiatric comorbidity, hippocampal sclerosis, a higher number of seizures occurring during monitoring, a history of seizure clusters, ASM taper rate, presurgical recording, a history of seizure-related injury, and treatment with

▼ Table 2. Independent determinants of LT-VEEG success show significant findings based on multivariable models. The number of studies that found the variable to be independently correlated with successful monitoring is listed, relative to the total number of studies that included the variable in multivariable analyses.

Factors determining the chance of success:	No. of studies showing significance/total no. of studies	References for significant findings
Baseline seizure frequency	2/2	[10, 24, 37]
ASM withdrawal	1/1	[18]
Shorter interval from the most recent seizure	1/1	[24]
Extra-temporal lobe epilepsy	1/1	[37]
ASM reduction not required	1/1	[24]

▼ **Table 3.** Adverse events in presurgical cases only.

Author (year)	No. of presurgical cases	No. of individuals with a non-habitual focal to bilateral tonic-clonic seizure during LT-VEEG	No. of individuals with a seizure cluster during LT-VEEG (cluster definition; >=3 per 4 or 24 hours)	No. of individuals with status epilepticus during LT-VEEG	No. of individuals with another seizure-related adverse event during LT-VEEG	Total rate of adverse events (no. of patients, %)
Cox *et al.* (2020) [15]	83	1 (1%)	1 (1%) in 24h	0	Falls: 2.0 (2%) Post-ictal psychosis: 1.0 (1%)	5 (6%)
Di Gennaro *et al.* (2012) [27]	54	4 (7%)	6 (11%) in 4h 21 (39%) in 24h	0	Falls: 3 (6%) Cardiac asystole: 0	13 (24%) 28 (52%)
Duy *et al.* (2020) [8]	114	3 (3%)	26 (23%) in 4h	2 (2%)	NR	31 (27%)
Fahoum *et al.* (2016) [20]	80	NR	NR	NR	NR	15 (19%)
Fung *et al.* (2018) [29]	69	NR	26 (79%) in 24h 7 (21%) non-habitual in 24h	2 (3%)	NR	NR
Guld *et al.* (2017) [11]	79	3 (4%)	24 (30%) in 4h 25 (32%) in 24h	7 (9%)	4 (5%): Bradycardia and respiratory arrest: 1 First Todd's paresis:1. Capillary oxygen saturation drop to 30%:1. Post-ictal psychosis-like symptoms:1	13 (16%)
Harini *et al.* (2013) [29]	95	NR	NR	2 (2%)	NR	NR
Haut *et al.* (2002) [32]	91	NR	56 (62%) in 24h	NR	NR	NR
Henning *et al.* (2014) [33]	60	2 (3%)	9 (15%) in 4h 25 (42%) in 24h	0	No seizure-related injuries	11 (18%)
Lim, *et al.* (2020) [37]	137	NR	2 (2%) in 1h	1 (1%)	Seizure cluster with post-ictal psychosis or dysphasia	3 (3%)
Yen, *et al.* (2001) [45]	89	8 (9%)	43 (48%) in 24h	0	NR	NR
Total	**951**	**24/473 (5%)***	**67/444 (15%) 4-h** **178/525 (34%) 24-h†**	**14/780 (2%)‡**	**12/413 (3%)§**	**106/607 (17%)**

Different definitions were used:
*total no. of individuals with non-habitual focal to bilateral tonic-clonic seizures during LT-VEEG (%).
† total no. individuals with seizure clusters during LT-VEEG based on three or more seizures during four hours and/or three or more seizures in 24 hours.
‡ total no. of individuals with status epilepticus during monitoring LT-VEEG.
§ total no. of individuals with other adverse events during LT-VEEG.
cumulative total rate individuals with one or more adverse events.
NR: not reported.

▼ **Table 4.** Risk factors shown to be independently related to the occurrence of adverse events during LT-VEEG. The number of studies that reported the variable is listed, relative to the total number of studies that included the variable in multivariable analyses.

Factors that determine the risk of an adverse event	No. of studies showing a significance/total no. of studies	References for significant findings
ASM tapering	2/7	[8,9]
History of SE	1/3	[28]
History of FBTCS	1/3	[9]
Psychiatric comorbidity	1/3	[28]
ASM taper rate	1/2	[9]
Hippocampal sclerosis	1/2	[32]
More events/seizures during monitoring	1/2	[20]
History of seizure cluster	1/1	[32]
Event/presurgical recording	1/1	[20]
History of seizure-related injury	1/1	[32]
Treatment with ASM in general		
Levetiracetam	1/1	[20]
Sulthiame	1/1	[20]

levetiracetam or sulthiame (*table 4*). ASM tapering was reported in most studies. In cases of ASM tapering, a distinction can be made between taper dose and taper rate, and based on multivariate analysis, taper dose was shown to affect the risk of an adverse to a greater extent than taper rate in two studies [8, 9].

Discussion

For presurgical LT-VEEG, the average yield – defined based on sufficient seizures being recorded or the clinical question answered – was 85%. Adverse events were reported in less than a fifth of the individuals. Independent determinants of successful monitoring were a high baseline seizure frequency, shorter intervals from the most recent seizure, no requirement to reduce ASM, and extratemporal lobe epilepsy. Adverse events were associated with several independent variables: ASM withdrawal, a previous history of SE, FBTC or seizure clusters, and more events occurring during monitoring.

We observed significant variation in the reported ASM withdrawal protocols, with notable differences in tapering speed. Most predefined protocols were individualised and based on characteristics such as baseline seizure frequency and history of status epilepticus or FBTC, which have been reported to influence the decision to withdraw or not, and the speed and dose of tapering [9-15]. Although several studies have shown that baseline frequency is an independent variable that determines the degree of success of LT-VEEG, another study suggested that there is no clinically significant relationship between self-reported baseline frequency and time to first seizure. However, the role of medication withdrawal in this study was unclear [16]. In our opinion, a minimal baseline seizure frequency should not be considered mandatory for referral for LT-VEEG, because ASM withdrawal also allows for successful monitoring in many patients with a low baseline frequency. Low seizure frequencies could, however, influence the individualized ASM withdrawal protocol [17]. In general, when deciding to apply seizure-provocation methods, benefits and risks need to be carefully balanced, and individuals and carers should be counselled. In this context, several studies have suggested that dose reduction contributes to the risk of adverse events more than tapering speed, and that adverse events occur more often during complete discontinuation or reduction to low ASM doses [8, 9]. FBTCS seemed to occur more often with ASM dose reduction to below 20-50% of the outpatient daily dose, depending on the history and frequency of FBTCS [8, 9]. Tapering speed, with a mean of 20% dose reduction (range: 0-100 %) during the first 24 hours, had no effect on length of stay, time to first seizure, or seizure type [8]. Another study, using a new protocol during the COVID-19 epidemic, with 50% dose reduction in the morning and complete discontinuation in the evening of the day prior to admittance, yielded more seizures in the first 24 hours, and led to a shorter length of stay, without a difference in complication rates, as compared to the authors' previously used protocol (when medication withdrawal was started on the second day after admission) [18]. This suggests that there could be a threshold dosage for safe and efficient ASM withdrawal during presurgical LT-VEEG. How such a threshold, including optimal taper rate, could be individually determined remains unclear. Since there were differences between children and adults with regards to frequency of medication withdrawal (more often in adults), duration of stay (longer in adults), and success rate (higher in children), it is advisable to develop separate protocols for both age groups. Another factor that needs to be explored is the different pharmacokinetics of ASMs and their specific effect on withdrawal-related LTM yield and risk of adverse events [19]. One study has shown that treatment with sulthiame or levetiracetam is an independent risk factor for adverse events [20]. These ASMs were more often used in polytherapy in this study, suggesting that the type of epilepsy was more refractory in these patients. To our knowledge, this finding has not yet been reproduced. Although tapering speed seems to have less influence on the rate of adverse events than absolute dose reduction, more rapid withdrawal will shorten the duration of LT-VEEG, which by itself has significant advantages concerning discomfort and available resources [9, 11, 18]. The timing of ASM withdrawal is still under-explored. Often when the individual is hospitalised, ASM withdrawal is only started at the onset of monitoring. Three studies have suggested that tapering over seven days before admission may contribute to successful monitoring without carrying additional risks [18, 22, 23].

This study has limitations which are inherent to a retrospective systematic review. Not all included studies presented useful data on yield and adverse events. First, the populations differed among studies; some reporting on only children, adults or the elderly. This could have influenced the average results as children are reported to have a shorter length of stay, a higher seizure frequency, and less often require ASM withdrawal than adults [24]. Second, most studies were descriptive or only applied univariate analyses. Only a few used multivariate analyses and the variables included in these prediction analyses differed. Some determinants were included, such as a continuous variable in one study and a categorised variable in another. Some of the variables were highly correlated but not reported as such. For example, many studies reported using individuals' baseline frequency when deciding whether or not ASM reduction was required, but these data were neither presented nor included in the multivariable analysis. It is remarkable that hyperventilation and sleep deprivation – both often considered effective provocation methods to increase the yield of LT-VEEG – were not found to be independently predictive of success in any of the studies included. Systematic inclusion of these methods in multivariable prediction analyses of LT-VEEG success in large cohorts could further clarify their added value as provocation factors in this setting. Third, there was considerable inconsistency between study results. Relatively small cohort sizes may limit the validity of predictors of success or adverse events, especially for those factors that show a weaker correlation. Fourth, there was a difference in the interpretation of specific variables among studies, and importantly, the observation that not all studies reported a seizure cluster as an adverse event may explain, in part, the significant variation in the total adverse event rate.

In conclusion, to identify all factors that independently contribute to the yield and risk of adverse events associated with presurgical LT-VEEG, more extensive studies with individual participant data and more appropriate statistics and standardization approaches are needed. Future work is warranted to develop guidelines for ASM withdrawal, taking into account predefined factors for success and risks, such as the timing of the withdrawal, speed and degree of dose reduction, and specific ASM pharmacokinetics. ■

Supplementary material.

Supplementary data and summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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TEST YOURSELF

(1) Which of the following factors has been reported to be an independent predictor of successful presurgical long-term video-EEG monitoring?

A. ASM withdrawal
B. Hyperventilation
C. High baseline frequency

(2) What is the average risk of an adverse event during presurgical long-term video-EEG monitoring?

A. $\sim$ 5%
B. $\sim$ 15%
C. $\sim$ 50%

(3) Which of the following has the greatest influence on risk of adverse events during ASM withdrawal?

A. Dose reduction
B. Taper speed
C. No difference

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