Examining the Seizure Standard for Commercial Motor Vehicle Drivers: Evidence Report, Systematic Review, and Medical Expert Panel Report

U.S. Department of Transportation
Federal Motor Carrier Safety Administration

June 2023

FOREWORD

Individuals with an established medical history or clinical diagnosis of epilepsy or any other condition that is likely to cause loss of consciousness or any loss of ability to control a commercial motor vehicle (CMV) are not allowed to operate a CMV in interstate commerce by Federal regulations. However, the Federal Motor Carrier Safety Administration (FMCSA) issues exemptions from the regulatory requirements for select drivers who meet criteria based primarily on long time periods of medical stability without a seizure.

Seven key questions are addressed in this report:

- The first five key questions address risk of seizure recurrence over time for individuals who have or have had unprovoked seizures, provoked seizures, a seizure caused by stroke, epilepsy, or surgery for epilepsy.
- The sixth key question addresses commercial driving requirements for each State in the United States and driving requirements generally for select other countries regarding seizures.
- The seventh key question, which provides recommendations for the current processes to address seizures among potential CMV drivers, was addressed by a medical expert panel.

This report is anticipated to be of interest to healthcare providers, insurers, employers, human resources personnel, State driver's licensing authorities, and FMCSA.

NOTICE

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Technical Report Documentation Page

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16. Abstract

Individuals with an established medical history or clinical diagnosis of epilepsy or any other condition that is likely to cause loss of consciousness or any loss of ability to control a commercial motor vehicle (CMV) are not allowed to operate a CMV in interstate commerce by Federal regulations. However, the Federal Motor Carrier Safety Administration (FMCSA) issues exemptions from the regulatory requirements for select drivers who meet criteria based primarily on long periods of medical stability without a seizure. This report includes systematic reviews that addressed key questions largely by published data, with an additional key question addressed by a medical expert panel. Five key questions address risk of seizure recurrence over time for individuals who have or have had unprovoked seizures, provoked seizures, a seizure caused by stroke, epilepsy, or surgery for epilepsy. Another key question addresses commercial driving requirements for each State in the United States and driving requirements generally for select other countries regarding seizures. A medical expert panel addressed questions concerning recommendations for the current processes to address seizures among potential CMV drivers. The medical expert panel determined there was no evidence to support major changes to the regulation or exemption criteria. However, several minor changes were advised, including multiple recommendations for clarifying definitions and the eligibility criteria for exemptions.

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SI* (MODERN METRIC) CONVERSION FACTORS

Approximate Conversions to SI Units				
Symbol	**When You Know**	**Multiply By**	**To Find**	**Symbol**
		Length		
in	inches	25.4	millimeters	mm
ft	feet	0.305	meters	m
yd	yards	0.914	meters	m
mi	miles	1.61	kilometers	km
		Area		
in^2	square inches	645.2	square millimeters	mm^2
ft^2	square feet	0.093	square meters	m^2
yd^2	square yards	0.836	square meters	m^2
ac	acres	0.405	hectares	ha
mi^2	square miles	2.59	square kilometers	km^2
		Volume (volumes greater than 1,000L shall be shown in m^3)		
fl oz	fluid ounces	29.57	milliliters	mL
gal	gallons	3.785	liters	L
ft^3	cubic feet	0.028	cubic meters	m^3
yd^3	cubic yards	0.765	cubic meters	m^3
		Mass		
oz	ounces	28.35	grams	g
lb	pounds	0.454	kilograms	kg
T	short tons (2,000 lb)	0.907	megagrams (or “metric ton”)	Mg (or “t”)
		Temperature (exact degrees)		
°F	Fahrenheit	5(F-32)/9 or (F-32)/1.8	Celsius	°C
		Illumination		
fc	foot-candles	10.76	lux	lx
fl	foot-lamberts	3.426	candela/m^2	cd/m^2
		Force and Pressure or Stress		
lbf	pound-force	4.45	newtons	N
lbf/in^2	pound-force per square inch	6.89	kilopascals	kPa

Approximate Conversions from SI Units				
Symbol	**When You Know**	**Multiply By**	**To Find**	**Symbol**
		Length		
mm	millimeters	0.039	inches	in
m	meters	3.28	feet	ft
m	meters	1.09	yards	yd
km	kilometers	0.621	miles	mi
		Area		
mm^2	square millimeters	0.0016	square inches	in^2
m^2	square meters	10.764	square feet	ft^2
m^2	square meters	1.195	square yards	yd^2
Ha	hectares	2.47	acres	ac
km^2	square kilometers	0.386	square miles	mi^2
		Volume		
mL	milliliters	0.034	fluid ounces	fl oz
L	liters	0.264	gallons	gal
m^3	cubic meters	35.314	cubic feet	ft^3
m^3	cubic meters	1.307	cubic yards	yd^3
		Mass		
g	grams	0.035	ounces	oz
kg	kilograms	2.202	pounds	lb
Mg (or “t”)	megagrams (or “metric ton”)	1.103	short tons (2,000 lb)	T
		Temperature (exact degrees)		
°C	Celsius	1.8c+32	Fahrenheit	°F
		Illumination		
lx	lux	0.0929	foot-candles	fc
cd/m^2	candela/m^2	0.2919	foot-lamberts	fl
		Force and Pressure or Stress		
N	newtons	0.225	pound-force	lbf
kPa	kilopascals	0.145	pound-force per square inch	lbf/in^2

* SI is the symbol for the International System of Units. Appropriate rounding should be made to comply with Section 4 of ASTM E380. (Revised March 2003, Section 508-accessible version September 2009)

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LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

Acronym	Definition
CCI	corpus callosum index
CDL	commercial driver's license
cEEG	continuous electroencephalography
CI	confidence interval
CINAHL	Cumulative Index to Nursing & Allied Health
CMV	commercial motor vehicle
COI	conflict of interest
CNS	central nervous system
CT	computed tomography
DMV	Department of Motor Vehicles
ECT	electroconvulsive shock therapy
EEG	electroencephalography
ES	early seizure
FMCSA	Federal Motor Carrier Safety Administration
FR	fast ripple
FS	febrile seizure
FTL	foreign tissue lesion
GSW	generalized spike-wave
GTCS	generalized tonic-clonic seizure
HEB	highly epileptiform burst
HR	hazard ratio
HS	hippocampal sclerosis
ILAE	International League Against Epilepsy
IQR	interquartile range

Acronym	Definition
LS	late seizure
MESS	Multicentre study of early Epilepsy and Single Seizures
MRI	magnetic resonance imaging
NFLE	nocturnal frontal lobe epilepsy
NCS	nonconvulsive seizure
NIHSS	National Institutes of Health Stroke Scale
PLED	periodic lateralized epileptiform discharge
PSS	post-stroke seizure
PSSE	post-stroke status epilepticus
PSSi	post-stroke seizure after ischemic stroke
PWE	person with epilepsy
RCT	randomized controlled trial
RNS	responsive neurostimulation
SANAD	standard and new antiepileptic drugs
SE	sleep epilepsy
S-GTCS	generalized tonic-clonic seizure during sleep
S-PE	partial epilepsy during sleep
SRHI	seizure-related head injury
TBI	traumatic brain injury
TGA	transient global amnesia
TLE	temporal lobe epilepsy
USDOD	U.S. Department of Defense
USDOT	U.S. Department of Transportation
WS	wake seizure

EXECUTIVE SUMMARY

PURPOSE

This technical report provides systematic reviews of the risks of seizure recurrence over time since the last seizure in specific groups of individuals affected by seizures. Studied groups include individuals who have or have had unprovoked seizures, provoked seizures, a seizure caused by stroke, epilepsy, and surgery for epilepsy.

This report includes requirements for each State in the United States and select other countries regarding seizures among drivers. It also provides medical expert panel recommendations for the current processes to address seizures among potential commercial motor vehicle (CMV) drivers.

PROCESS

This technical report represents a comprehensive initial examination of seven key questions identified by the Federal Motor Carrier Safety Administration (FMCSA). The seven questions are:

1. What is the risk for seizure recurrence after an unprovoked first seizure at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and more than 10 years following the first seizure for individuals who (a) are treated with antiepileptic drugs, and (b) are not treated with antiepileptic drugs?
2. What is the risk for seizure recurrence after a provoked first seizure at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and more than 10 years following the first seizure for individuals who (a) are treated with antiepileptic drugs, and (b) are not treated with antiepileptic drugs?
3. What is the risk for seizure recurrence after a seizure caused by stroke at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and more than 10 years following the first seizure for individuals who (a) are treated with antiepileptic drugs, and (b) are not treated with antiepileptic drugs?
4. What is the risk for seizure recurrence after a diagnosis of epilepsy at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and more than 10 years following the diagnosis for individuals who (a) are treated with antiepileptic drugs, and (b) are not treated with antiepileptic drugs?
5. What is the risk for seizure recurrence for individuals who have undergone surgery for a structural brain abnormality or epilepsy at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and more than 10 years following the surgery?
6. What are the requirements for each State in the United States concerning seizures among commercial drivers? What are the driving requirements generally for select other countries?
7. What are the medical expert panel recommendations regarding seizures and driving for commercial drivers including (a) following a first unprovoked seizure, (b) following a first provoked seizure, (c) following a diagnosis of epilepsy, and

(d) following a diagnosis of sleep epilepsy (defined as epilepsy with seizures only while asleep or upon awakening)?

The first five key questions above were each addressed with a systematic review. Key question 6 was addressed for each State in the United States and the District of Columbia by searching in legal databases and department of motor vehicle (DMV) websites and by calling States to obtain additional information. Throughout the report, "State" refers to any of the 50 States and the District of Columbia. International requirements were obtained from website sources only. Answering key question 7 required seeking expert opinions, although a systematic review was also performed to address risks among individuals with sleep epilepsy.

To address the first five key questions, systematic searches were performed using five search engines. The following electronic databases were searched:

- PubMed
- Scopus
- Cumulative Index to Nursing & Allied Health (CINAHL)
- Cochrane Library
- Google Scholar

Searches incorporated specific Medical Subject Heading Terms to focus on the most relevant reports. The terms "study" and "report" are used in this document. A study has a specific research design and typically produces at least one report (i.e., "a publication"). There may be more than one report from a given study, particularly if there is longer term follow-up that occurs (e.g., 1-year report, 5-year report). Websites of Federal agencies, including the U.S. Department of Transportation (USDOT) and U.S. Department of Defense (USDOD), were also searched as were any report's references to additional reports.

RATIONALE AND BACKGROUND

Seizures and epilepsy impact an estimated 0.5 percent of the worldwide population, with approximately 2 million individuals affected in the United States.[1 2] Both the prevalence and incidence rates vary markedly across the population. Incidence rates are bimodal, with the highest among the youngest and oldest segments of the population. (See references 3, 4, 5, 6, 7, 8, and 9.)

Different countries and States have varying requirements regarding driving with a history of seizures. Yet most requirements do not differentiate by seizure type, even while listing different requirements for drivers with epilepsy. (See references 10, 11, 12, 13, 14, 15, 16, and 17.)

A FMCSA regulation states in part that an individual is physically qualified to drive a CMV in interstate commerce if the individual has "no established medical history or clinical diagnosis of epilepsy or any other condition which is likely to cause loss of consciousness or any loss of ability to control a commercial motor vehicle."[18] However, FMCSA issues exemptions from

this regulation for select drivers who meet criteria based primarily on long periods of medical stability without a seizure.[19]

This study is needed to identify and review the body of medical literature (particularly literature with longer follow-up periods) addressing the risks of seizure recurrence. There also have been advances in surgery for epilepsy that warrant further analyses. A compilation of updated regulations by State is also potentially useful, particularly for FMCSA.

STUDY FINDINGS

Key findings for each key question are summarized below.

Key Question 1: Unprovoked Seizures

There are 19 reports to address key question 1(a) and 5 reports to address key question 1(b). These studies show consistent data from multiple populations, including both randomized and longitudinal observational data. Based on these studies, the risk of seizure recurrence over time after a first unprovoked seizure is a hyperbolic function: a rapid initial decrease in risk that is followed by a slower decrease. There is also a high degree of confidence that the same type of mathematical risk relationship is present regardless of whether the individual is treated with an antiepileptic drug or not.

Key Question 2: Provoked Seizures

As defined by the International League Against Epilepsy (ILAE), a provoked seizure is synonymous with a "reactive seizure," an "acute symptomatic seizure," or a "seizure that is provoked by a transient factor acting on an otherwise normal brain to temporarily lower the seizure threshold."[20] Under this definition of provoked seizure, there are no data of sufficient quality to address risk of seizure recurrence after a provoked seizure. (See key question 3 regarding risk among individuals having incurred strokes, which are not considered here as provoked seizures.)

Key Question 3: Seizures Caused by Strokes

There are eight studies that address key question 3. There are many causes of seizure following a stroke, and for nearly all those causes there are no quality studies regarding quantified risk over time of seizure recurrence. Based on the small body of published literature, there is low confidence in a quantitative predictability of seizures after a first seizure caused by stroke, aside from some evidence that the late occurrence of seizure after stroke predicts higher risk of recurrence. Available studies do not define well whether the studied patients are treated with antiepileptic drugs.

Key Question 4: Epilepsy

There are 26 reports addressing seizure recurrence risk over time among those with antiepileptic drug treatment (key question 4(a)). There are five reports addressing key question 4(b) with risk over time among those with untreated epilepsy. There are consistent data from multiple populations documenting the risk of seizure recurrence over time after a prior diagnosis of epilepsy is a hyperbolic function. Most of the risk for recurrence is in the first year after a

seizure. There is also a high degree of confidence that the same type of mathematical risk relationship is present regardless of whether the individual is treated with antiepileptic drugs. However, the magnitudes of risks are higher among those untreated.

Key Question 5: Post-Surgical Seizures

There are eight studies that help partially address key question 5, including varying diagnoses. All studies report high rates of seizure recurrences, ranging from 34 to 70 percent, with the best results due to only 2 years of follow-up data.[21] Thus, there is moderately high confidence that seizure recurrences are common among post-surgical patients treated surgically for refractory epilepsy. However, the highest quality study included surgeries performed prior to 1999. Also, most studies did not report antiepileptic drug usage.

Key Question 6: Driving Requirements

Searches were performed to examine (a) how requirements vary among States regarding commercial driving in relation to seizures, and (b) how other countries regulate driving generally in relation to seizures. The State searches were conducted by searching legal databases, including Casetext and Justia, and State DMV websites and by calling States for additional information. There are some States that have intrastate commercial driver certification regulations regarding seizures.

Key Question 7: Expert Recommendations

A medical expert panel addressed key question 7. The full discussion of the results is detailed later in the report. The medical expert panel determined that the findings did not include evidence strong enough to support major changes to the regulation or exemption criteria, but several minor changes were advised. The panel advised that the regulation be clarified to provide that the prospective driver not have a current diagnosis of epilepsy. The word “current” would be an addition. The panel also recommended that the issue of multiple epileptogenic foci should be distinguished in the exemption criteria. There were several areas where the panel recommended clarifying definitions and the eligibility criteria for exemptions.

CONCLUSIONS

Seizure recurrence risk varies by seizure classification (e.g., provoked seizure, unprovoked seizure, epilepsy, post-surgical). Where quality research has been published, risk for seizure recurrences in all cases decreases with time since the last seizure. The medical expert panel determined there was no evidence to support major changes to the regulation or exemption criteria. However, several minor changes were advised, including multiple recommendations for clarifying definitions and the eligibility criteria for exemptions.

1. INTRODUCTION

Seizures and epilepsy impact an estimated 0.5 percent of the worldwide population, with approximately 2 million individuals affected in the United States.[22 23] Epilepsy may be associated with cognitive and visual impairments and may be difficult to treat, especially among safety-critical workers such as drivers because the adverse effects of antiepileptic drugs also include cognitive impairments. (See references 24, 25, 26, 27, and 28.) Also, reductions in neuropsychological function after surgery for epilepsy have been suggested.[29]

Both the prevalence and incidence rates of seizures and epilepsy vary markedly across the population. Incidence rates are bimodal, with the highest rates among the youngest and oldest segments of the population. (See references 30, 31, 32, 33, 34, and 35.) The degree of impairment with seizures depends greatly on the type of seizure (e.g., generalized or focal). Classifications can be further delineated according to features and length of the seizure. Some individuals experiencing generalized seizures will have an additional period of pre-ictal activity (i.e., impaired function and confusion that immediately precedes the seizure).[36 37] Conversely, an individual experiencing a focal seizure may remain conscious but undergo a period of significant impairment of physical and/or mental function during and after the seizure. Focal seizures may also progress to generalized seizures with loss of consciousness. (See references 38, 39, 40, 41, and 42.)

Different countries and States have varying requirements regarding driving with a history of seizures. Yet most requirements do not differentiate by seizure type, even while listing different requirements for drivers with epilepsy. (See references 43, 44, 45, 46, 47, 48, 49, and 50.) A FMCSA regulation states in part that an individual is physically qualified to drive a CMV in interstate commerce if the individual has "no established medical history or clinical diagnosis of epilepsy or any other condition which is likely to cause loss of consciousness or any loss of ability to control a commercial motor vehicle."[51] However, FMCSA issues exemptions from this regulation for select drivers who meet criteria based primarily on long periods of medical stability without a seizure.[52]

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2. RESEARCH METHODOLOGY

2.1 SEARCH METHODOLOGY

The systematic reviews and evidence report were developed using standard search methods to address the first five key questions. Key question 6 was addressed for each State by searching in legal databases and State DMV websites and by calling States to obtain additional information. International requirements were obtained only from website sources. Key question 7 required expert opinions, although a systematic review was also performed to address risks among individuals with sleep epilepsy.

To address the first five key questions, systematic searches were performed using five search engines. The following electronic databases were searched:

- PubMed
- Scopus
- Cumulative Index to Nursing & Allied Health (CINAHL)
- Cochrane Library
- Google Scholar

Searches incorporated specific Medical Subject Heading terms to focus on the most relevant reports. The terms "study" and "report" are used in this document. A study has a specific research design and typically produces at least one report (i.e., "a publication"). There may be more than one report from a given study, particularly if there is longer term follow-up that occurs (e.g., 1-year report, 5-year report). Websites of Federal agencies, including the USDOT and USDOD, were also searched as were any report's references to additional reports. Identified reports were retrieved and only full-length reports were reviewed to determine whether the requisite data were provided to answer that specific key question.

Where appropriate, a meta-analysis was performed. All retrieved reports were assessed for data availability to answer key questions for seizure recurrence figures. Reports that did not have recurrence figures were excluded from meta-analysis. Data from each individual study were aggregated to the following months: 6, 12, 18, 24, 36, 48, 60, and 72. Each relative contribution was weighted by the sample size of the original report at each specific time point. Incidences were computed for each period of month(s). Curves were plotted graphically. The equation of the curvilinear line along with R^2 values were also calculated to allow for prediction of recurrence chance at future time points.

Limitations of a meta-analysis approach are grounded in the soundness of the individual studies subjected to meta-analysis. Particularly, biases in the underlying studies, limitations in number of studies, small sample sizes, and overall methodological weaknesses (e.g., weaknesses in the capture of seizures) typically drive weaknesses in meta-analyses. In the case of the meta-analyses contained in this technical report, due to the varying number and quality of studies that were involved in each meta-analysis, there are varying amounts of confidence in resulting estimates.

Existing weaknesses are believed to primarily concern adequacy of sample sizes as the other factors are not believed to be heavily influential in this set of literature. This report denotes an overall qualitative interpretation of the confidence in the meta-analysis estimates.

2.2 INCLUSION/EXCLUSION CRITERIA

Each report that was identified using the search terms was reviewed against inclusion criteria. To be included, a report had to contain all data needed to address the relevant key question. Inclusion criteria did not include a specific date range. Included studies must have analyzed adult subjects, defined for this study as someone 18 or order. Studies were also included that analyzed both adults and children combined.[1] Age distribution of participants was noted in study summaries in as much detail as possible. Prior to review, a report had to meet the following criteria:

- Be published in English.
- Be available in full-length and not a letter, editorial, news, comment, case report, review, note, abstract, or conference paper.
- Describe a study that enrolled 10 or more subjects.

After review of the full-length publications, the included reports were abstracted into tables of evidence. Each report was reviewed, scored, and critically appraised. Randomized controlled trials were scored using both the GRADE[(53)] and American College of Occupational and Environmental Medicine's[(54)] scoring systems. Observational studies were scored using the Ottawa-Newcastle scoring system.[(55 56)] Non-randomized interventional trials or descriptive studies (e.g., consecutive case series) are not scored; however, they were summarized and may be included for help to provide information to answer some questions.

During the search, Medical Subject Heading Terms were used to specifically address each question. The terms included convulsions, seizure, or epilepsy, along with seizure recurrence risks. Along with those terms, additional terms such as incidence, prevalence, cohort, longitudinal, population, population-based, or clinical trials were added. To find additional surgery-based reports the term "post-surgery" was used for that specific question.

These terms returned 55 reports that varied in their approaches and the types of seizures being analyzed. Many of the reports included more than one type of seizure. In total there were 20 reports of non-specified or mixed seizure types, 2 on refractory epilepsies, 2 on sleep epilepsy, 2 on temporal lobe epilepsy, 2 on drug-resistant focal epilepsy, 11 on unspecified epilepsy, 4 on idiopathic seizures, 8 on tonic-clonic seizures, 1 on post-stroke seizures, 1 on post-trauma seizures, and 2 on single seizures.

[1] Studies that combined adults and children were used in this systematic review and meta-analysis as: (1) older children appear to have comparable seizure histories and experiences as adults, and (2) the overall literature base is sparse, thus omission of too many studies results in much lower confidence in risk estimates while likely excluding many meaningful cases.

2.3 MEDICAL EXPERT PANEL AND PROCESSES

A five-member medical expert panel was convened to address issues raised by the key questions. Panel members were provided a draft of this report. The panel met via videoconference and addressed key question 7. It also provided comments and opinions on the report and other aspects of the research literature, clinical practice, and CMV driver policies. Panel members also provided recommendations to FMCSA that are elsewhere in this report.

The five panel members were:

Proleta Datta, MD, PhD
Assistant Professor
Department of Neurology
Oregon Health & Sciences University
Portland, Oregon

William W. Greaves, MD, MSPH, FACOEM
OEM Associates
Milwaukee, Wisconsin

Sindhu Richards, MD
Assistant Professor
Department of Neurology
University of Utah

Matthew Rizzo, MD, FAAN
Professor and Chair
Department of Neurological Sciences
University of Nebraska-Omaha

Jon Tippin, MD
Adjunct Clinical Professor
Department of Neurology
University of Iowa Hospitals and Clinics
Iowa City, Iowa

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3. EVIDENCE SUMMARY

3.1 KEY QUESTION 1: UNPROVOKED SEIZURES

What is the risk for seizure recurrence after an unprovoked first seizure at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and more than 10 years following the first seizure for individuals who (a) are treated with antiepileptic drugs, and (b) are not treated with antiepileptic drugs?

There are 19 reports that address key question 1(a) and 5 reports that address key question 1(b). Included reports for 1(a) are: Aktekin 2006; Bonnett 2010; Bonnett 2017; Chadwick 1996; Das 2000; Donselaar 1992; First Seizure Group 1993; Haltiner 1997; Hart 1990; Hauser 1990; Hauser 1998; Hesdorffer 2009; Hopkins 1988; Hui 2001; Kim 2006; Kho 2006; Kumar 2019; Musicco 1997; and Punia 2015. Included studies for 1(b) are Bonnett 2017; Das 2000; Donselaar 1992; First Seizure Group 1993; and Musicco 1997. See Appendix A for summaries of the reports.

Most study designs were prospective cohort studies, but three were randomized trials. The three randomized clinical trials evaluated immediate compared with delayed treatment with an antiepileptic drug and followed these groups of patients over time. These are the most powerful studies to address these questions, particularly as the follow-ups were of long duration and captured seizure recurrence risks over time.

The FIRST Seizure Trial Group was a randomized clinical trial of immediate compared with delayed antiepileptic drug treatment among 419 patients who had a first tonic-clonic seizure. The study found early treatment did not improve prognosis, as 50 percent of those sustaining a first seizure did not experience a second during the 4-year follow-up period.[57] This study included risks over time, so the FIRST study has the requisite data to address key questions 1(a) and 1(b).

The Multicentre study of early Epilepsy and Single Seizures (MESS) trial was a randomized clinical trial of immediate compared with delayed antiepileptic drug treatment among 1,847 patients who had an initial tonic-clonic seizure or early epilepsy. This study found 43 percent of the immediate treatment group compared with 53 percent of the deferred group sustained a second seizure, suggesting minimal benefit from early antiepileptic drug treatment compared with observation. By 8 years, 46 percent of the immediate group compared with 52 percent of the delayed group had sustained seizures.[58]

A randomized clinical trial with 76 patients in India compared immediate with delayed antiepileptic drug treatment. Long seizure duration, family history of seizures, and electroencephalography (EEG) abnormalities predicted increased risk of recurrence.[59]

Non-randomized, observational studies of longitudinal case series of patients are considered the next strongest study design available. These have been reported from many different populations of patients.

The National General Practice Study of Epilepsy was based in the United Kingdom and was a prospective longitudinal case series of 564 patients. This study found 46 to 78 percent sustained

a second seizure over a 2-year period.[60] However, the data included some patients treated after the first seizure (15 percent).

A longitudinal case series of 310 untreated patients from Hong Kong followed over 4 years found that approximately 30 percent incurred a second seizure in the first year and another 17 percent incurred a second seizure over the subsequent 3 years.[61]

A longitudinal case series of 208 patients from Minnesota having had one unprovoked seizure found increased risk of recurrence if there was a sibling with epilepsy, and/or there were EEG abnormalities, although there was no stratification by antiepileptic drug use.[62] Another longitudinal case series of 204 patients from Minnesota having had two unprovoked seizures, most of whom were treated with antiepileptic drugs, found the time to seizure recurrence was faster as the number of seizures incurred increased.[63]

There are consistent data from multiple populations and including both randomized and longitudinal observational data documenting that the risk of seizure recurrence over time after a first seizure decreases along a hyperbolic curve (see Figure 1), declining swiftly and then more gradually. There is also a high degree of confidence that the same type of mathematical risk relationship is present regardless of whether the individual is treated with antiepileptic drugs. The main differences are that the use of antiepileptic drugs results in a less steep slope as the drugs appear to reduce risk of seizure in the short-term but less so over the longer term.

These studies' data were combined in a meta-analysis to estimate the risk of seizure recurrence among individuals sustaining a first unprovoked seizure treated and untreated with antiepileptic drugs at specific intervals. Results are provided in Table 1. The risk estimates are calculated by taking the population known to have been seizure-free for the prior interval (e.g., 2183 were seizure free for 18 months upon entering the 18-month time frame) and using that population count as the denominator. The numerator is the new seizures amongst this previously seizure-free group (n equals 257), resulting in a period-specific incidence rate of 11.77 percent. For example, if someone is seizure-free for 18 months, there is an 11.77 percent risk they will incur a seizure recurrence in that next interval of 6 months. Tables of recurrent seizure risk for different study questions describe the meta-analysis where studies with data at specific time intervals were combined to create a more stable estimate of risk.

Column 1 is the time interval being assessed. Column 2 is the sum total of the number of individuals in each study within each specific timeframe. Column 3 is the sum total of recurrent seizures from each report included in the meta-analysis. Column 4 is the crude individual risk estimate for each time point as a proportion of the total within that time point. The last column is a predicted risk at that time point estimated from the meta-analysis. This last column fits the data to a curve by assigning a "best fit" function along the entire range, creating a curve to estimate the risk.

Reports followed up at different time points such as annually or biannually, and in some cases had more rigorous follow-up procedures. Therefore, the sample in a specific time frame can be less than or greater than the previous time frame.

Table 1. Relationship of seizure recurrence by time since a first unprovoked seizure.

Time interval	Sample in this time frame (n)	Number with recurrent seizures (n)	Individual risk estimate at each time point (%)	Predicted risk from equation (%)
6 months	4429	1258	28.50%	25.85%
12 months	4195	794	22.72%	19.73%
18 months	2183	257	11.77%	15.06%
24 months	2450	232	9.77%	11.50%
36 months	1094	84	6.57%	6.70%
48 months	810	19	4.30%	3.90%
60 months	427	10	2.81%	2.28%
72 months	280	3	1.07%	1.33%

Figure 1 shows the relationship of seizure recurrence by time for individuals sustaining a first unprovoked seizure treated and untreated with antiepileptic drugs. The x-axis is the time interval (Column 1), and the y-axis is the individual risk estimate at each time point (Column 4). Included reports for the meta-analysis are: Aktekin 2006; Bonnett 2010; Bonnett 2017; Chadwick 1996; Das 2000; Donselaar 1992; First Seizure Group 1993; Haltiner 1997; Hart 1990; Hauser 1990; Hauser 1998; Hesdorffer 2009; Hopkins 1988; Hui 2001; Kim 2006; Kho 2006; Kumar 2019; Musicco 1997; and Punia 2015.

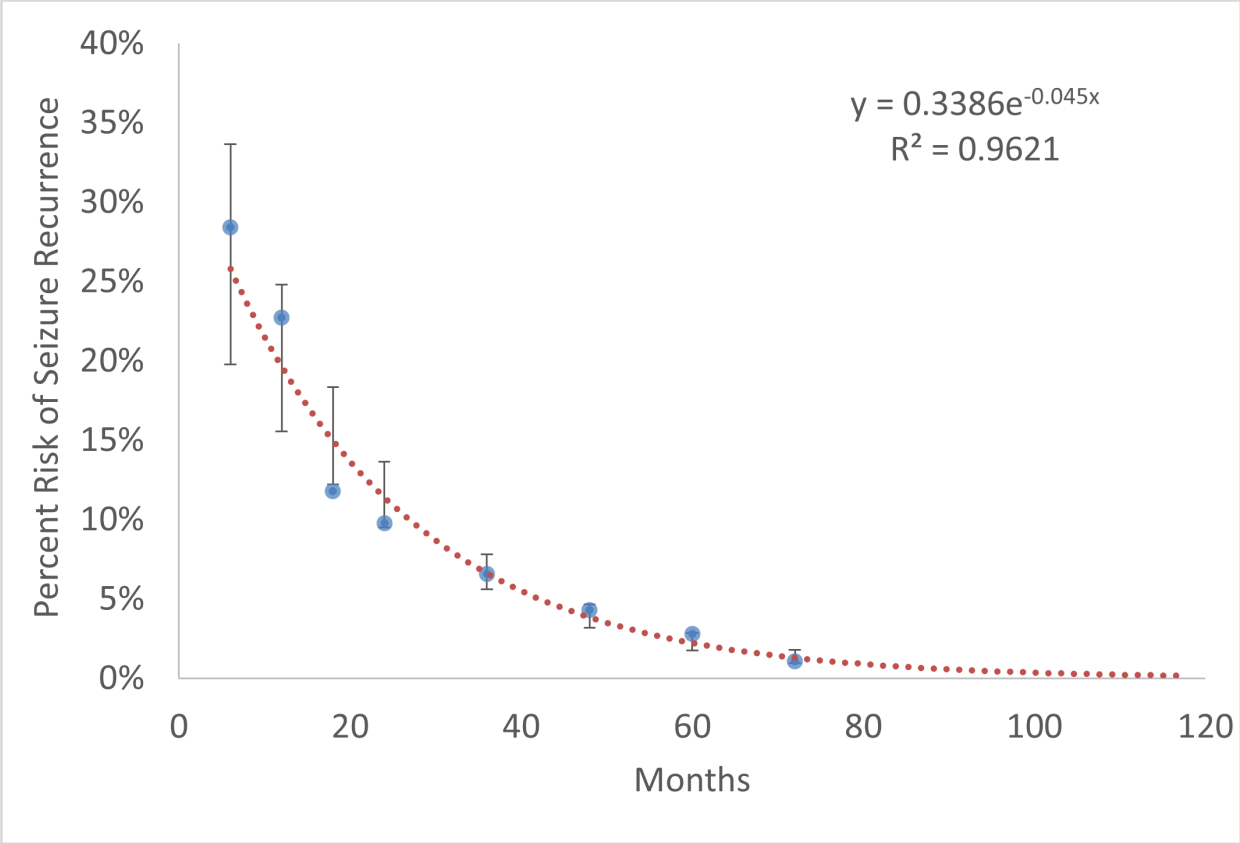

Figure 1. Relationship of seizure recurrence by time since a first unprovoked seizure.

Figure 2 shows the seizure recurrence by time in months since a first unprovoked seizure for individuals treated with antiepileptic drugs. Here, risk estimates are calculated as described previously. The x-axis is the time interval, and the y-axis is the individual risk estimate at each time point. Included reports for the meta-analysis are: Bonnett 2017; First Seizure Group 1993; and Musicco 1997.

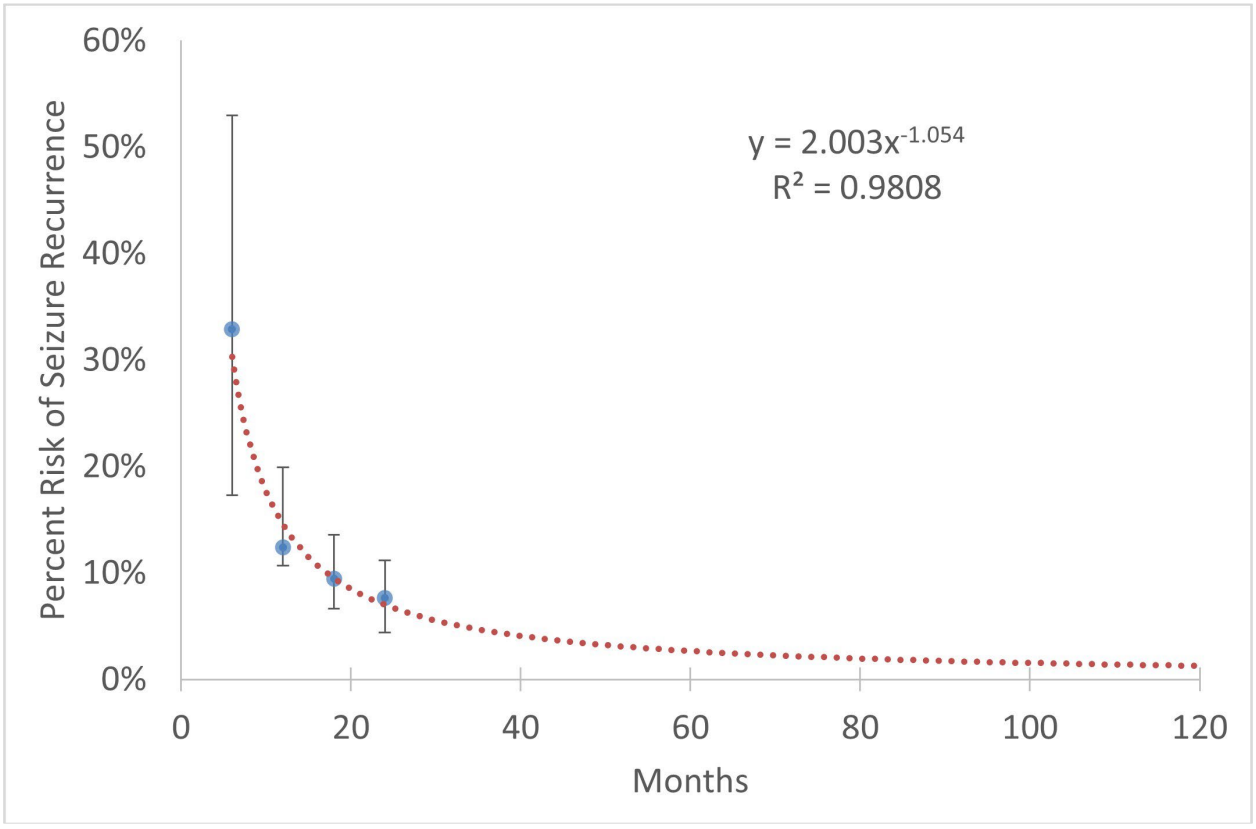

Figure 2. Relationship of seizure recurrence by time since a first unprovoked seizure for treated individuals.

3.2 KEY QUESTION 2: PROVOKED SEIZURES

What is the risk for seizure recurrence after a provoked first seizure at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and more than 10 years following the first seizure for individuals who (a) are treated with antiepileptic drugs, and (b) are not treated with antiepileptic drugs?

As defined by the International League Against Epilepsy (ILAE), a provoked seizure is synonymous with a "reactive seizure," an "acute symptomatic seizure," or a "seizure that is provoked by a transient factor acting on an otherwise normal brain to temporarily lower the seizure threshold."[64] Under this definition of provoked seizure, i.e., a seizure involving reversible and/or avoidable causes, there are no data of sufficient quality to address risk of seizure recurrence after a provoked seizure.

3.3 KEY QUESTION 3: SEIZURES CAUSED BY STROKES

What is the risk for seizure recurrence after a seizure caused by stroke at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and more than 10 years following the first seizure for individuals who (a) are treated with antiepileptic drugs, and (b) are not treated with antiepileptic drugs?

There are eight studies that address key question 3. The literature and practical observations identify many causes of seizure following a stroke. For nearly all the causes, there are no quality studies regarding quantified risk over time of seizure recurrence. Available studies do not define well whether the studied patients are treated with antiepileptic drugs. Studies included are: Devinsky 1983; Kho 2006; Chadwick 1996; Kim 2016; Berges 2000; Tomari 2017; Kotsopoulos 2005; and Park 1998. See Appendix C for summaries of the reports.

A longitudinal case series of 497 patients found a provoked etiology of the seizures predicted an 88 percent higher risk of recurrence over the following 12 months (OR = 1.88, p = 0.02).[65] A retrospective longitudinal case series of 81 patients found there were heterogenous causes of provoked seizures and many recurrences over variable lengths of time.[66] A registry-based study of seizures in stroke patients found risks for seizure recurrence included atrial fibrillation, male sex, and a large cortical stroke.[67]

A registry-based case series of 159 patients found that late onset seizures after strokes (more than 14 days) predict a higher risk of seizure recurrence.[68] A longitudinal case series of 153 patients with a post-stroke seizure found late occurrence of the seizure to predict higher risk of stroke and seizure recurrence.[69]

There is low confidence in the quantitative predictability of seizures after a first seizure provoked by stroke. For post-stroke seizures, there is some evidence that late occurrence of seizure predicts higher risk of recurrence.

Due to (i) widely differing underlying causes, (ii) individual case heterogeneity, (iii) rapidly advancing treatment approaches and techniques for some of the causes, (iv) heterogeneity of the literature, and (v) few studies reporting risk over time in sufficient detail, the meta-analysis is limited to the small body of published literature on seizures caused by strokes. With such limited data, the confidence in the risk estimates is low for key question 3. The risk estimates are calculated by taking the population known to have been seizure-free for the prior interval and using that as the denominator while the numerator is the new seizures amongst this group previously seizure-free for a period-specific incidence rate.

Individuals included in the meta-analysis are based on data provided from each individual report. Reports utilized follow up at different time points, and in some cases had more rigorous follow-up procedures. Therefore, the sample in the specific time frame does not always decrease over time.

Table 2. Relationship of seizure recurrence by time since a seizure provoked by stroke.

Time interval	Sample in this time frame (n)	Number with recurrent seizure(s) (n)	Individual risk estimate at each time point (%)	Predicted risk from equation (%)
6 months	626	247.6	39.55%	39.89%
12 months	1296	495	38.19%	34.13%
18 months	No Data	No Data	Not Applicable	29.18%
24 months	670	114	19.94%	24.98%
36 months	258	55	21.32%	18.29%
48 months	107	14	13.08%	13.39%

Figure 3 shows the seizure recurrence by time in months since a first seizure provoked by stroke. Here, risk estimates are calculated as described previously. The x-axis is the time interval, and the y-axis is the individual risk estimate at each time point. Included reports are: Devinsky 1983; Kho 2006; Chadwick 1996; Kim 2016; Berges 2000; Tomari 2017; Kotsopoulos 2005; and Park 1998.

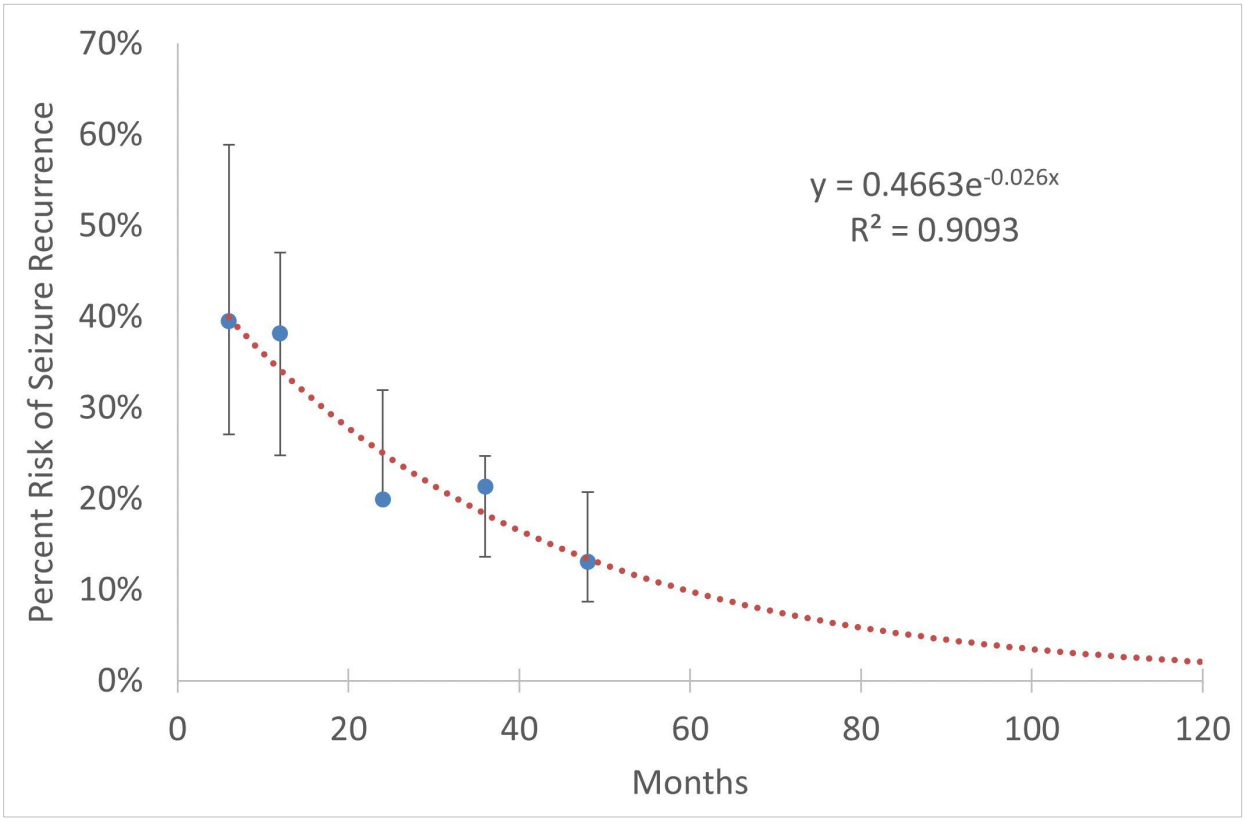

Figure 3. Relationship of seizure recurrence by time since a seizure provoked by stroke.

3.4 KEY QUESTION 4: EPILEPSY

What is the risk for seizure recurrence after a diagnosis of epilepsy at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and more than 10 years following the diagnosis for individuals who (a) are treated with antiepileptic drugs, and (b) are not treated with antiepileptic drugs?

There are 26 reports addressing seizure recurrence risk over time among individuals with antiepileptic drug treatment (key question 4(a)). Included reports for question 4(a) are: Tanaka 1992; Lossius 1999; Punia 2015; Kim 2006; Kim 2016; Abraira 2019; Arena 2017; Choi 2008; Schiller 2009; Marson 2005; Friedman 2012; Lhatoo 2001; Cardoso 2003; Beghi 1988; Kalita 2005; MRCADWS 1991; Specchio 2001; Callaghan 1988; Heller 1995; Elwes 1984; Nakazawa 1995; Kotsopoulos 2005; Bonnett 2010; Bonnett 2017; Chadwick 1996; and Kumar 2019. There are five reports addressing key question 4(b) with risk over time among individuals with untreated epilepsy. The included reports for question 4(b) are: Kim 2006; Marson 2005; Heller 1995; Elwes 1984; and Specchio 2001. See Appendix D for summaries of the reports.

One clinical trial, the Medical Research Council Antiepileptic Drug Withdrawal Study (MRCADWS), randomly divided patients on antiepileptic drugs into groups that maintained treatment and groups that discontinued treatment. This study produced multiple reports.[70 71 72] One of the reports included risk of recurrence over time in the discontinuation group.[73] It found no change in the prognosis of the epilepsy, and about 45 percent of the patients had had seizure recurrence by 3.25 years. Data are provided by year. Ongoing follow-up of the study found no change in prognosis of the epilepsy, but there was increased risk of recurrence especially in the first 1 to 2 years after discontinuation of the antiepileptic drug.

A randomized trial of various antiepileptic drugs found no differences in rates of seizure remission at 3 years of follow-up among the antiepileptic drug used (phenobarbitone phenytoin, carbamazepine, or sodium valproate).[74] A prospective longitudinal case series of 256 consecutive patients in a long-term remission found seizure recurrence in 40.2 percent by 5 years and 25.3 percent developed drug-resistant epilepsy.[75] However, clear data to address risk on and off antiepileptic drugs over time were not provided.

A non-randomized comparative trial reported risks of seizure among individuals with slow antiepileptic withdrawal compared with no withdrawal.[76] The probability of remaining seizure-free at 5 years was 50 percent with slow antiepileptic withdrawal compared with 75 percent with no withdrawal. The British National General Practice Study of Epilepsy found most patients with epilepsy enter a remission; however, it did not clearly distinguish individuals using and not using antiepileptic drugs. A retrospective longitudinal case series of 669 patients found increased risk of seizure recurrence among those over 50 years of age, but the study did not provide risk by year.[77]

A population-based study in the United Kingdom found approximately 20 percent of newly diagnosed patients with epilepsy have “inadequate control” and approximately 30 percent have a treatment change by 10 years; risk by time stratified by antiepileptic drug use was not provided.[78] A prospective longitudinal case series found individuals on polypharmacy experienced faster recurrences.[79] However, clear data to address risk on and off antiepileptic

drugs over time were not provided. Another prospective longitudinal case series of 106 patients found that the risk of recurrence was highest in the first 2 years.[80]

A trial of 94 patients comparing full versus partial antiepileptic drug withdrawal found seizure recurrence was 34 percent versus 33 percent, respectively.[81] A prospective longitudinal case series of 283 patients found risk of seizure recurrence among those with epilepsy was 36 percent at 3 months and 49 percent at 1 year.[82] A prospective longitudinal case series of 120 consecutive patients with epilepsy found that 75 percent of patients achieved a remission of 1 year and most were on single antiepileptic drug therapy.[83] A longitudinal case series of 94 patients who were seizure-free for at least 2 years found that 31 relapsed within 6 to 62 months.[84] A longitudinal case series of 43 individuals who were seizure-free for at least 2 years where antiepileptic drugs were then withdrawn completely found none relapsed once the antiepileptic drug was discontinued during the follow-up period (mean of 4.8 years).[85]

There are consistent data from multiple populations documenting that the risk of seizure recurrence over time after a prior diagnosis of epilepsy is a hyperbolic function, with most of the risk for recurrence in the first year after a seizure. Further, there is also a high degree of confidence that the same type of mathematical risk relationship is present regardless of whether the individual is treated with an antiepileptic drug or not. However, the magnitudes of risks are higher among those untreated. The use of an antiepileptic drug results in a less steep slope.

Table 3 represents a combination of the studies' data in a meta-analysis, showing the risk of seizure recurrence at specific intervals among those diagnosed with epilepsy who are treated or untreated with antiepileptic drugs. Figure 4 shows the relationship of seizure recurrence among individuals with epilepsy who are treated or untreated with antiepileptic drugs, and Figure 5 shows this relationship for treated individuals. Risk estimates are calculated by taking the population known to have been seizure-free for the prior interval and using that as the denominator, while the numerator is those with new seizures amongst this group previously seizure-free for a period-specific incidence rate.

Table 3. Meta-analysis of seizure recurrence risk for treated or untreated epilepsy.

Time interval	Sample in this time frame (n)	Number with recurrent seizure(s) (n)	Individual risk estimate at each time point (%)	Predicted risk from equation (%)
6 months	4429	1258	27.78%	26.55%
12 months	4195	794	20.61%	15.70%
18 months	2183	257	5.58%	11.54%
24 months	2450	232	10.00%	9.28%
36 months	1094	84	8.35%	6.83%
48 months	810	19	8.35%	5.49%
60 months	427	10	5.33%	4.63%
72 months	280	3	2.67%	4.04%

Figure 4 shows the seizure recurrence by time in months for individuals with epilepsy who are treated and not treated with antiepileptic drugs. Here, risk estimates are calculated as described previously. The x-axis is the time interval, and the y-axis is the individual risk estimate at each time point. Included reports are: Tanaka 1992; Lossius 1999; Punia 2015; Kim 2006; Kim 2016;

Abraira 2019; Arena 2017; Choi 2008; Schiller 2009; Marson 2005; Friedman 2012; Lhatoo 2001; Cardoso 2003; Beghi 1988; Kalita 2005; MRCADWS 1991; Specchio 2001; Callaghan 1988; Heller 1995; Elwes 1984; Nakazawa 1995; Kotsopoulos 2005; Bonnett 2010; Bonnett 2017; Chadwick 1996; and Kumar 2019.

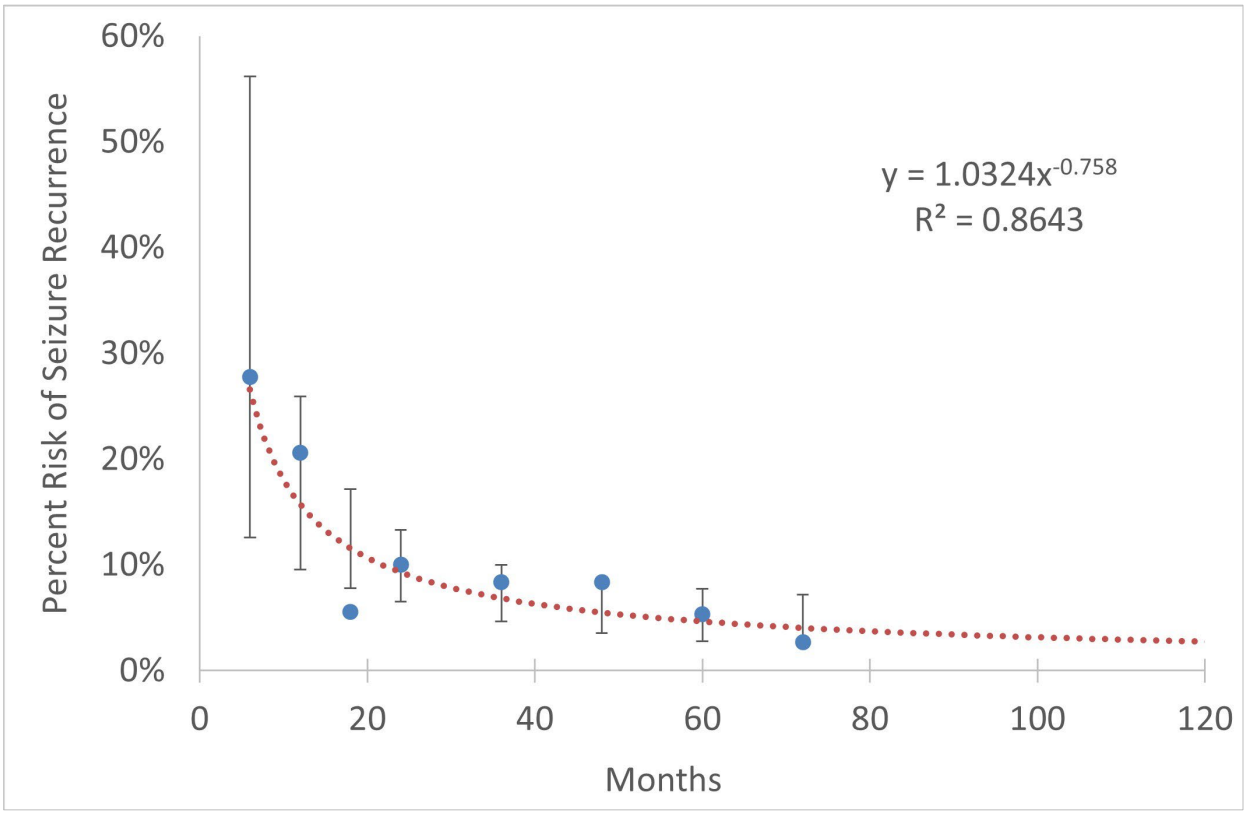

Figure 4. Relationship of seizure recurrence among individuals with epilepsy who are treated or untreated.

Figure 5 shows the seizure recurrence by time in months for individuals with epilepsy who are treated with antiepileptic drugs. Here, risk estimates are calculated as described previously. The x-axis is the time interval, and the y-axis is the individual risk estimate at each time point. The included reports are: Kim 2006; Marson 2005; Heller 1995; Elwes 1984; and Specchio 2001.

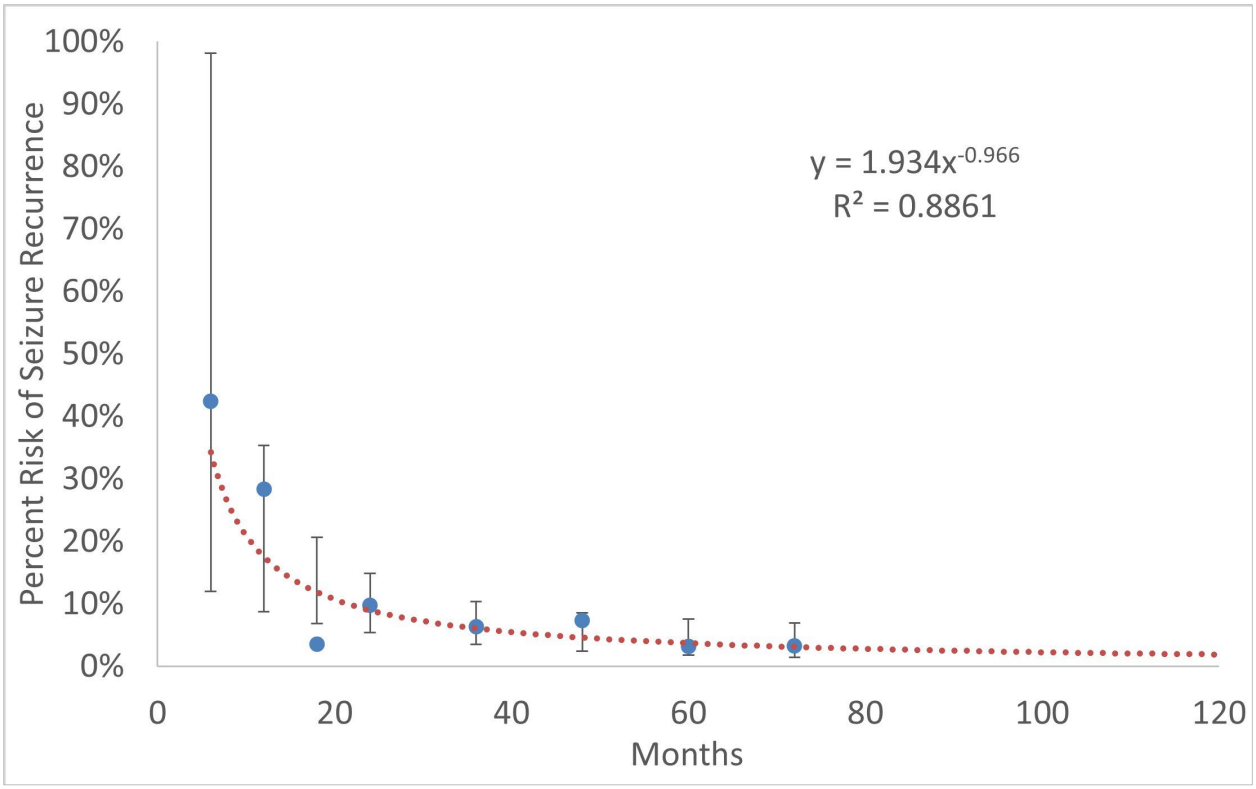

Figure 5. Relationship of seizure recurrence among individuals with epilepsy who are treated.

3.5 KEY QUESTION 5: POST-SURGICAL SEIZURES

What is the risk for seizure recurrence for individuals who have undergone surgery for a structural brain abnormality or epilepsy at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and more than 10 years following the surgery?

There are eight studies that help partially address key question 5, including varying diagnoses. All studies report high rates of seizure recurrences, ranging from 34 to 70 percent, with the best results due to only 2 years of follow-up data.[86] Thus, there is moderately high confidence that seizure recurrences are common among post-surgical patients treated surgically for refractory epilepsy. However, the highest quality study included surgeries performed prior to 1999. Also, most studies did not report antiepileptic drug usage. See Appendix E for summaries of the reports.

A longitudinal case series of 325 patients who underwent temporal lobectomy between 1978 and 1998 for temporal lobe epilepsy found widely varying prognoses for seizure-free status over 20 years.[87] The best prognosis was for foreign tissue lesion (approximately 55 percent seizure-free, graphic interpretation), followed by hippocampal sclerosis (approximately 25 percent seizure-free, graphic interpretation). These were followed by "normal," "other," and "distant lesion" (0 percent).

A longitudinal case series of 615 patients included patients who underwent anterior temporal lobe resections (495) and patients who underwent other surgical procedures. The data suggested

48 percent of the population sustained seizures while 52 percent did not sustain seizures within 5 years post-surgery.[88] A longitudinal case series of 55 patients having undergone temporal lobectomy reported approximately 70 percent incurred seizures within 5 years while approximately 30 percent were seizure-free for 5 years.[89]

A longitudinal case series of 99 patients with partial seizures found 56 (79 percent) were seizure-free at 6 months, 53 (75 percent) at 1 year, and 47 (66 percent) were seizure-free at 2 years.[90] A longitudinal case series of 61 heterogenous causes of neocortical temporal lobe epilepsy found improvements after surgery for neocortical temporal lobe epilepsy, although absolute rates over time were not reported.[91]

A meta-analysis was not judged to be scientifically sound for key question 5. While such an analysis is technically feasible, its value and usefulness are limited by several factors: (i) widely differing underlying causes, (ii) rapidly advancing surgical approaches and techniques, (iii) varying surgical procedures used, (iv) some reporting of outcomes as improvement in epilepsy without absolute seizure rates, (v) unclear antiepileptic drug use, as well as (vi) heterogeneity of the literature. Therefore, this report does not include a meta-analysis for question 5.

3.6 KEY QUESTION 6: DRIVING REQUIREMENTS

What are the commercial driving requirements for each State in the United States concerning seizures? What are the driving requirements generally for select other countries?

Searches were performed to examine (a) how requirements vary among States regarding commercial driving in relation to seizures, and (b) how select other countries regulate driving generally in relation to seizures.

The State searches were conducted by searching in legal databases, such as Casetext and Justia, and State DMV websites and by calling States for additional information. There are some States that have intrastate commercial driver certification requirements regarding seizures, and those have been indicated in Appendix F.

The country searches were simpler and examined only the amount of time required to be seizure free before a driver's license could be obtained. These requirements are also provided in Appendix F.

3.7 KEY QUESTION 7: EXPERT RECOMMENDATIONS

What are the medical expert panel recommendations regarding seizures and driving for commercial drivers including (a) following a first unprovoked seizure, (b) following a first provoked seizure, (c) following a diagnosis of epilepsy, and (d) following a diagnosis of sleep epilepsy (defined as epilepsy with seizures only while asleep or upon awakening)?

The medical expert panel was queried about potential biases in the literature. This was requested as biases are not always apparent or identifiable other than by content experts. Further, moderate to strong weaknesses may invalidate conclusions from systematic reviews and meta-analyses.

The medical expert panel noted the definition of epilepsy has evolved, and the current epidemiological database necessarily relies on studies from prior definitions.

The medical expert panel found that in non-randomized trials, it is possible that the individuals prescribed antiepileptic drugs may be perceived to have higher risks for recurrence and that despite attempts to omit individuals with higher risk (e.g., EEG abnormalities), a residual bias may be present. Some studies were noted to include some individuals with probable epilepsy. The randomized trials would likely negate most of these concerns among those studies.

Regarding a first unprovoked seizure, there is no major identifiable, strong bias in the available studies; available studies thus likely produce reasonably reliable risk estimates. Although the non-randomized studies may have some selection of higher risk patients into the treated group, the medical expert panel determined based on the systematic reviews and meta-analysis that there are no evidence-based data on which to recommend changes to the current FMCSA seizure exemption criteria.

The medical expert panel noted regarding a first provoked seizure (defined as something caused by a reversible/avoidable factor, e.g., medication, severe hypoglycemia from poor diabetic control) that there are many specific, individual factors. The medical expert panel determined there is no significantly increased recurrence risk for individuals incurring a provoked seizure when the seizure was due to a reversible factor and that factor is eliminated or otherwise avoided.

The medical expert panel found that there are many causes of seizure following a stroke and that these cases are quite heterogenous. For nearly all causes, there is a limited ability to quantify risk of seizure recurrence over time with evidence-based data. Regardless, individuals incurring a late seizure due to stroke should be presumed to have epilepsy.

While the current ILAE classification system has 63 types of seizures, there are fewer types that are important for distinguishing appropriateness for driving. As well, the classification system is heavily dependent on the initial manifestations (focal, generalized, unknown; awareness; motor manifestations). These initial manifestations, while having some relationships to treatment, have little relationship to qualifications to drive.

Prior to 2014, epilepsy was defined as 2 or more unprovoked or reflex seizures at least 24 hours apart. Since 2014, epilepsy has been defined by the ILAE as a disease of the brain defined by any of the following conditions: (1) at least 2 unprovoked (or reflex) seizures occurring more than 24 hours apart; (2) 1 unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60 percent) after 2 unprovoked seizures, occurring over the next 10 years; or (3) diagnosis of an epilepsy syndrome. Epilepsy is now classified by the ILAE as resolved when an individual has been both seizure free for 10 years and off antiepileptic drugs for 5 or more years. The medical expert panel recommended that FMCSA adopt the ILAE definition for when epilepsy is resolved.

The medical expert panel stated it would have been helpful if the literature had stratified age at onset before/after approximately age 25, as tapering studies may have been addressing various seizure disorders of childhood. The medical expert panel found there is insufficient data regarding typical individuals with epilepsy who are off antiepileptic drugs, particularly as the standard of care is for them to be treated with these medications.

The medical expert panel also found regarding a diagnosis of epilepsy that there is no identifiable, strong bias in the available studies, so those studies produce reliable risk estimates. There are some concerns that individuals who were selected for treatment may represent a higher risk group. Yet those randomized trials may ameliorate these concerns. Based on the systematic review and meta-analyses, the medical expert panel determined that there are no evidence-based data on which to recommend changes to the current FMCSA seizure exemption criteria. However, the panel advised the criteria regarding not having had a seizure "for 8 years" be clarified to "at least 8 years" prior to certification. In addition, it was advised that the regulation be clarified for the prospective driver to not have a "current" diagnosis of epilepsy. The medical expert panel recommended that the issue of multiple epileptogenic foci should be distinguished in the criteria. The medical expert panel found that such individuals are not appropriate candidates for CMV driving.

Regarding surgery for epilepsy, the medical expert panel stated there are now many surgical procedures, most of which, however, have no associated quality data to provide risk estimates to answer this key question. The available studies provide some risk estimates, particularly for temporal lobe epilepsy, and those recurrence risk estimates are high. Temporal lobe epilepsy surgery also can result in visual field deficits (e.g., quadrantanopia) that also should be considered as it may limit safe CMV driving. Based on the systematic review, the medical expert panel found that there are no evidence-based data on which to recommend changes to the current FMCSA regulation or exemption criteria.

Regarding sleep epilepsy, a systematic review was performed. A longitudinal case series of 161 patients followed over 2 to 6 years found a risk of awake seizures to be 13 percent (95 percent CI 7–18 percent) over 6 years, while among individuals without risk factors (sudden withdrawal of therapy and more frequent sleep seizures) to be 6.5 percent (95 percent CI 1.5–11.3 percent).[92] One longitudinal case series of 55 patients found 17 (30.9 percent) sustained at least one seizure while awake over at least a 10-year follow-up period.[93] Studies suggest risk of awake seizures among those with sleep epilepsy is estimated at 13 to 31 percent. Thus, the data are consistent with a significant risk of conversion from only sleep epilepsy to sustaining a seizure while awake. The medical expert panel determined that the risks of conversion of sleep epilepsy to a seizure occurring while awake were too high to advise changes in the current FMCSA seizure exemption criteria. See Appendix G for summaries of the reports.

Section 5 provides additional findings and recommendations in the Medical Expert Panel Report.

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4. CONCLUSIONS

Seizure recurrence risk varies by seizure classification (e.g., provoked seizure, unprovoked seizure, epilepsy, post-surgical). Where quality research has been published, risk for seizure recurrences in all cases decreases with time since the last seizure.

With respect to unprovoked seizures, there are consistent data from multiple populations and including both randomized and longitudinal observational data documenting that the risk of seizure recurrence over time after a first unprovoked seizure is a hyperbolic function. There is also a high degree of confidence that the same type of mathematical risk relationship is present regardless of whether the individual is treated with antiepileptic drugs. The main differences are that the use of antiepileptic drugs results in a less steep slope as the drugs appear to reduce risk of seizure in the short-term but less so over the longer term.

A provoked seizure can be considered as being synonymous with a "reactive seizure," an "acute symptomatic seizure," or a "seizure that is provoked by a transient factor acting on an otherwise normal brain to temporarily lower the seizure threshold." When using this definition of provoked seizure, there are no quality data to address risk of seizure recurrence after a provoked seizure.

There are many causes of seizure following a stroke, and for nearly all causes there are no high-quality studies regarding quantified risk over time of seizure recurrence. Based on the small body of published literature, there is low confidence in a quantitative predictability of seizures after a first seizure caused by stroke, aside from some evidence that late occurrence of seizure after stroke predicts higher risk of recurrence.

With respect to a prior diagnosis of epilepsy, there are consistent data from multiple populations documenting the risk of seizure recurrence over time is a hyperbolic function. Most of the risk for recurrence is in the first year after a seizure. There is also a high degree of confidence that the same type of mathematical risk relationship is present regardless of whether the individual is treated with antiepileptic drugs or not. However, the magnitudes of risks are higher among those untreated.

With respect to surgically treated epilepsy, all studies report high rates of seizure recurrences ranging from 34 to 70 percent. The better results are likely due to only 2 years of follow-up data. Thus, there is moderately high confidence that seizure recurrences are common among post-surgical patients treated surgically for refractory epilepsy.

Searches were performed to examine (a) how requirements vary among States regarding commercial driving in relation to seizures; and (b) how select other countries regulate driving generally in relation to seizures. The State searches were conducted by searching in legal databases, including Casetext and Justia, and State DMV websites and by calling States for additional information. There are some States that have intrastate commercial driver certification requirements regarding seizures.

The medical expert panel helped address key question 7. The medical expert panel determined that the findings did not include evidence strong enough to support major changes to the regulation or exemption criteria, but several minor changes were advised. The medical expert

panel advised that the regulation be clarified for the prospective driver to not have a current diagnosis of epilepsy. The panel also recommended that the issue of multiple epileptogenic foci should be distinguished in the exemption criteria. There were several areas where the panel recommended clarifying definitions and the eligibility criteria for exemptions.

5. MEDICAL EXPERT PANEL REPORT

The medical expert panel findings and recommendations for evaluating potential CMV drivers who have or have had a seizure or epilepsy include:

1. Regarding a first unprovoked seizure—based on systematic reviews and meta-analysis, there are no evidence-based data on which to recommend changes to the current FMCSA seizure exemption criteria.
2. Regarding a first provoked seizure (defined as a seizure that is provoked by a transient factor acting on an otherwise normal brain to temporarily lower the seizure threshold)—while there are no quality data on which to quantify risk, there is no significantly increased recurrence risk for individuals incurring a provoked seizure when the seizure was due to a reversible factor and that factor is eliminated or otherwise avoided.
3. Regarding a seizure after stroke—there are many causes of seizure following a stroke and these causes are heterogenous. There is a limited ability to quantify risk of seizure recurrence over time. Regardless, those incurring a late seizure due to stroke should be presumed to have epilepsy.
4. Regarding epilepsy—based on systematic reviews and meta-analysis, there are no evidence-based data on which to recommend changes to the current FMCSA seizure exemption criteria. However, modifying the criteria regarding not having had a seizure "for 8 years" to "at least 8 years" prior to certification is suggested.
5. Regarding surgery for epilepsy—there now are many surgical procedures, though most of which have no associated quality data to provide risk estimates. The available studies provide some risk estimates, particularly for temporal lobe epilepsy, and those risk estimates for seizure recurrences are high. Temporal lobe epilepsy surgery also can result in visual field deficits (e.g., quadrantanopia) that also should be considered as it may limit safe CMV driving. Due to data heterogeneity, a meta-analysis would not be scientifically sound. There are no evidence-based data on which to recommend changes to the current FMCSA regulation or exemption criteria.
6. Regarding sleep epilepsy—based on the systematic review, the risks of conversion from sleep epilepsy to a seizure while awake were too high to advise changes in the current FMCSA seizure exemption criteria.

Given the findings and recommendations for evaluating potential CMV drivers who have or have had a seizure or epilepsy, recommendations for further research and additional considerations are provided by the medical expert panel:

7. Regarding provoked seizures with a provoking factor within the individual's control (e.g., alcohol for an alcohol-induced seizure), it is advised that FMCSA specify no use of the provoking factor for a specified amount of time.
8. Regarding provoked seizures due to illicit drug(s) and/or alcohol, it is advised that clarification be provided that the prospective driver needs to be off the drug(s)/alcohol for a specified amount of time, as well as under control by treatment.

For medication-induced provoked seizures, it is advised that clarification be provided that the prospective driver needs to be off the medication.

9. It is suggested that the term "provoked seizure" be clearly defined as a seizure that is caused by a reversible and/or avoidable factor acting on otherwise normal brain tissue. Thus, if the reversible factor (e.g., a medication that lowers the seizure threshold) or avoidable factor (e.g., alcohol) can be avoided, the risk of seizure is equivalent to that of a non-affected person. After a person incurs a provoked seizure and the reversible and/or avoidable factor is removed, there is no need for further preclusion from driving beyond five half-lives to sufficiently clear a provoking drug.
10. Examples of low-risk recurrence of a provoked seizure are suggested to be provided (e.g., on a provoking medication and now off that medication, seizures that were caused by a medication). There is some potential confusion regarding what a provoked seizure is. There appears to be a potential for a medical examiner to allow someone to drive who does not have normal brain tissue and the seizure risk of an average driver. Thus, it is advised that the examples of provoked seizure and criteria for allowing an individual to drive a CMV be clear and explicit. The following criteria are advised:
    - There is no history of seizure(s) prior to or after the single provoked seizure.
    - The seizure occurred after either (a) a drug known to cause seizures, (b) an avoidable metabolic condition (e.g., low glucose, low sodium), (c) alcohol or illicit drug withdrawal, or (d) within 24 hours after a non-penetrating head injury that included not more than 30 minutes of loss of consciousness.
    - The factor (e.g., drug, metabolic condition) is fully reversed, removed, and avoidable.
    - If the seizure was caused by a drug, at least five half-lives have lapsed after the last dose of the drug prior to medical certification.
    - If an EEG was performed, it is normal.
    - If magnetic resonance imaging (MRI) or a CT was performed, the brain tissue is normal.
11. There are online risk calculators being developed for seizures, which may be helpful in some circumstances, particularly when validated.
12. As some individuals may have had a remote diagnosis of epilepsy in childhood, it is advised that the FMCSA regulation be changed to not having a "current" diagnosis of epilepsy.
13. Antiepileptic drugs may cause cognitive impairment, and those potential impairments should be assessed and integrated into a decision by a qualified neurologist regarding whether to allow a prospective CMV driver to drive.
14. For prospective drivers with epilepsy, drug-drug interactions should be considered by FMCSA and evaluated by a qualified neurologist, as these interactions could compound impairments.
15. Definitions of seizures and epilepsy continue to evolve. It is recommended these definitions be considered to clarify the existing guidance.

16. There are several surgical procedures and devices used for the treatment of epilepsy. It is recommended that these procedures and devices, including responsive neurostimulation (RNS), undergo systematic reviews for seizure recurrence risks. RNS feedback systems have objective measures of seizures that need to be integrated, from both neurology and FMCSA standpoints, into decisions regarding whether to allow a prospective CMV driver to drive.

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APPENDIX A: SEIZURE RECURRENCE RISK AFTER FIRST UNPROVOKED SEIZURE, WITH AND WITHOUT ANTIEPILEPTIC DRUG TREATMENT

Author, Year Score: 3*	Kumar, 2019, Acta Neurol Scand; Unprovoked; Treated Title: Seizure recurrence risk in persons with epilepsy undergoing antiepileptic drug tapering. Seizure Types: Focal onset and generalized onset seizures (myoclonic excluded).
Category	Seizure
Study Type	Observational study
Conflict of Interest	Sponsored by (partial) funding from Project A-428 Institute Research Grant via All India Institute of Medical Sciences in New Delhi. No COI.
Sample Size	N = 438 persons with epilepsy (PWE) undergoing antiepileptic drug tapering.
Age/Sex	Mean age: 25.4 years, no other data about age. 245 males, 163 females.
Comparison	Group 1: PWEs who were receiving monotherapy including antiepileptic drugs such as valproate (VPA, up to 60 mg/kg tapering off), carbamazepine (CBZ, up to 35 mg/kg tapering off), phenytoin (PHT, up to 6 mg/kg tapering off), levetiracetam (LEV, up to 60 mg/kg tapering off), or clobazam (CLB, max dose not included) (n = 181) vs. Group 2: PWEs who were receiving polytherapy involving the same antiepileptic drugs listed above (n = 227).
Follow-Up	Follow-up ranging from 19–41 months.
Results	Examining the level of seizure recurrence risk in PWEs found no difference between types of therapy. Group 1 had 25.9% vs. Group 2 at 31.7% (p = 0.09). Both groups' risk for seizure recurrence was highly related to characteristics such as history of smoking (p = 0.003), history of failing antiepileptic drug tapering (p = 0.04), frequency of seizures (p = 0.002), and duration of epilepsy (p = 0.03).
Conclusion	"There is a wide variation in antiepileptic drug tapering pattern and seizure recurrence risk can be minimized by considering the risk factors like history of smoking/alcohol/tobacco, longer duration of epilepsy, frequency of seizures before control, and previously failed tapering."
Comments	Prospective longitudinal case series regarding tapering. Up to 3.5 years of follow-up study.

Author, Year Score: 5.0	Bonnett, 2017, BMJ; MESS trial, secondary analysis; Unprovoked; Treated Title: Risk of a seizure recurrence after a breakthrough seizure and the implication for driving: Further analysis of the standard versus new antiepileptic drugs (SANAD) randomized controlled trial. Seizure Types: Epileptic seizures; mention of myoclonic, absence, and tonic-clonic seizures.
Category	Antiepileptic drugs: carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate, valproate
Study Type	Secondary analysis of randomized controlled trial (RCT)
Conflict of Interest	Sponsored by National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care, Northwest Coast. No COI.

Sample Size	N = 399 patients greater than 16 years of age who had a history of at least 2 clinically significant epileptic seizures within the last year, had no seizure for 12 months when receiving treatment, and had maintained or increased medication dosage 6 months before having a breakthrough seizure.
Age/Sex	Mean age: Not provided. Median age: 38.3 years (Interquartile range (IQR) 24.3–53.5 years, all above 16 years old.) 231 males, 168 females.
Comparison	Single group comprised of participants from both Arm A and Arm B of the SANAD RCT. (N = 286) patients came from Arm A, which consisted of 1721 patients assigned to carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate in a 1:1:1:1:1 ratio vs. (n = 113) came from Arm B, which consisted of 716 patients assigned to valproate (considered as the standard of care), lamotrigine, or topiramate in a 1:1:1 ratio.
Follow-Up	1 month, 2 months, 6 months, 1 year, and 2 years.
Results	Probability of a seizure by 12 months was 70.1%. The number of people and the percentage of the population that had a seizure by the specified period is: 1 month - 111 people (28%), 2 months - 166 people (42%), 6 months - 214 people (54%), 1 year - 242 people (61%), 2 years – 254 people (64%). At 6 months the risk of having another seizure is significantly greater than 20%. At 12 months the risk of having another seizure is significantly less than 20% based on a 95% confidence interval (CI).
Conclusion	"Twelve months appears to be an appropriate time off driving for patients of driving age who have experienced a period of at least 12 months initial seizure freedom followed by a breakthrough seizure. Provided that patients remain seizure-free for 12 months following a breakthrough seizure, their risk of a seizure in the next 12 months would be less than the 20% risk standard that informs the UK legislation and [Driver and Vehicle Licensing Agency] guidance."
Comments	RCT of comparing antiepileptic drugs for those with 2 or more unprovoked seizures in past year. Combined analyses. Two arms differed by family history (8% vs. 19%), seizure type, EEG, CT, and age at first breakthrough seizure.

Author, Year Score: 4.5	Musicco, 1997, Neurology; Unprovoked; Treated/Untreated Title: Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy. Seizure Types: Tonic-clonic.
Category	Patients with tonic-clonic seizures are placed into medication treatments
Study Type	RCT
Conflict of Interest	Supported by Ciba-Geigy, Italy. No mention of COI.
Sample Size	N = 419 people who had an unprovoked primary or secondary seizure.
Age/Sex	Age: 114 below 16, 277 between 16–60, and 28 above 60, no other age data are reported. 236 males, 183 females.
Comparison	Patients who were randomized into an immediate antiepileptic medication trial, namely benzodiazepines (n = 215) vs. patients who were treated when seizures occurred (n = 204).
Follow-Up	Follow-up after 1 and 2 years.

Results	In the first 6 months, 52 of the 215 patients experienced seizure relapse and 85 out of the 204 had a relapse. For treated patients, only 17% experienced relapse after 1 year and 26% after 2 years. For untreated, 37% experienced relapse after 1 year and 45% after 2 years. (Adjusted RR = 0.5, 95% CI 0.3–0.6). Remission was more likely after 1 year for those untreated (RR = 1.2, 95% CI 0.97–1.56).
Conclusion	"In conclusion, our study showed that treating patients with a first unprovoked seizure was associated with a 50% reduction in the risk of relapse."
Comments	Second report of study (for First Seizure Trial Group). Data suggest treatment of minimal benefit after first tonic-clonic seizure.

Author, Year Score: 2.5	Chadwick, 1996, Epilepsia; Provoked/Unprovoked; Treated Title: Outcomes after seizure recurrence in people with well-controlled epilepsy and the factors that influence it. Seizure Types: All types.
Category	Medications, seizures
Study Type	Longitudinal case series study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 409 patients with recurrent seizures.
Age/Sex	No mention of age or sex.
Comparison	Patients were placed on antiepileptic drugs and were monitored for 6 months to see how often recurrences occurred. If patients were to die the study would cease from following that patient, but still include them.
Follow-Up	Follow-up after 6 months, 1 year, and 2 years.
Results	Of all the patients, 51% of them were able to remain seizure-free (95% confidence limits 45, 56%) within the first year and 40% within 2 years (95% confidence limits 35, 45).
Conclusion	"Our results provide no evidence that discontinuation of antiepileptic drugs modifies the long-term prognosis of a person's epilepsy, although it does increase the risk of seizures in the 1- to 2-year period after discontinuation."
Comments	Data suggest reduced risk of recurrence among those on antiepileptic drugs.

Author, Year Score: 5.5	Bonnett, 2010; Unprovoked, BMJ; Treated/Untreated; Secondary Analysis of MESS Trial Title: Risk of recurrence after a first seizure and implications for driving: Further analysis of the multicenter study of early epilepsy and single seizures. Seizure Types: Early epilepsy and single seizures.
Category	Seizure
Study Type	RCT
Conflict of Interest	Sponsored by grants from the National Institute for Health Research. No mention of COI.
Sample Size	N = 1,443 patients with single unprovoked seizures.
Age/Sex	No mention of mean age or sex.
Comparison	Immediate Treatment: Patients received immediate treatment for single unprovoked seizures vs. Delayed Treatment: Patients received delayed treatment for single unprovoked seizures.
Follow-Up	Follow-up at 6, 12, 18, and 24 months.

Results	Patients in the immediate treatment group had a 14% risk of seizure recurrence after a seizure-free period of six months (95% CI (CI: 10–18%) compared to 18% risk of seizure recurrence in the delayed treatment group (95% CI: 13–23%). After 12 months, the delayed treatment group had a risk of 10% (95% CI: 6–15%).
Conclusion	"After a seizure-free period of six months following a first seizure the overall risk of a recurrence was low enough (below 20%) to allow people to resume driving, irrespective of whether they had started antiepileptic."
Comments	Third report of MESS trial

Author, Year Score: 3.5	Das, 2000; Unprovoked, Neurol India; Treated/Untreated Title: Risk of recurrence of seizures following single unprovoked idiopathic seizure. Seizure Types: Unprovoked idiopathic seizures.
Category	Seizure
Study Type	RCT
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 76 patients with a single seizure occurrence that was unprovoked.
Age/Sex	No mention of mean age. 56 males, 20 females.
Comparison	Treated Group: Patients received antiepileptic drugs and EEG to assess for generalized spike and wave patterns, repetition and rate, focal epileptiform activity, focal slowing, nonspecific theta, or delta slowing (n = 36) vs. Untreated Group: Patients received only EEG (n = 40).
Follow-Up	Follow-up monthly for 3 months, quarterly for 1 year, and at 1.5 years.
Results	Proportion of patients with seizure recurrence in patients with abnormal vs. normal EEG: 12/16 vs. 10/60 ($p < 0.001$). Proportion of patients with seizure recurrence in treated vs. untreated group: 4/36 vs. 18/40 ($p < 0.002$). Proportion of patients with recurrence in patients with vs. without family history of seizures: 6/10 vs. 16/16 ($p < 0.05$).
Conclusion	"Patients of a single unprovoked idiopathic seizure with a normal CT scan are less likely to have a recurrence if the duration of seizure at presentation is short, EEG is normal, more than 3 months have passed since the first seizure and if treatment has been started. Family history of seizures does have a moderately significant bearing, but alcohol intake does not increase the chances of seizure."
Comments	RCT of antiepileptic drugs for unprovoked.

Author, Year Score: N/A	Kho, 2006; Provoked/Unprovoked, Neurology; Treated/Untreated Title: First seizure presentation: Do multiple seizures within 24 hours predict recurrence? Seizure Types: None specified.
Category	Seizure
Study Type	Longitudinal case series study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 497 patients with a first seizure occurrence.
Age/Sex	Mean age: 40.5 years. 322 males, 175 females.

Comparison	Study Group: Patients with two or more seizures separated by a recovery period within 24 hours (n = 72) vs. Comparison Group: Patients with a single seizure (n = 425). 97% of all patients received an EEG and 95% received neuroimaging.
Follow-Up	Follow-up at 12 months.
Results	Number (percent) of patients with generalized tonic-clonic seizures in Study vs. Comparison Group: 64 (96%) vs. 408 (96%). Prediction of multiple seizures based on odds ratio for older age (95% CI): 1.02 (1.01, 1.03), (p = 0.005) and based on provoked etiology: 1.88 (1.08, 3.22), (p = 0.02). Mean Age (years) for Study Group vs. Comparison Group: 43 vs. 38 (p = 0.01). Number (percent) of provoked seizures for Study vs. Comparison Group: 26 (36%) vs. 111 (26%), (p = 0.05). Number (percent) of Focal for Study vs. Comparison Group: 13 (19%) vs. 33 (8%), (p = 0.007). Number (percent) patients treated after first seizure for Study vs. Comparison Group: 38 (53%) vs. 89 (21%), (p < 0.001).
Conclusion	"Overall, treated patients had a higher seizure recurrence rate, irrespective of whether they were in the single- or multiple-seizure groups. This is consistent with the strong correlation of factors influencing the decision to start treatment and factors predictive of recurrence, including remote symptomatic etiology."
Comments	Case-control study. Multiple seizures within 24 hours found unlikely to predict recurrence. As to 45-55-year-olds treated with antiepileptic drugs, conclusions tentative.

Author, Year Score: 2*	Hopkins, 1988; Unprovoked, Lancet; Treated/Untreated Title: The first seizure in adult life. Value of clinical features, electroencephalography, and computerized tomographic scanning in prediction of seizure recurrence. Seizure Types: Tonic-clonic or partial seizures.
Category	Seizure
Study Type	Prospective study
Conflict of Interest	Sponsored by A. H., a Wolfson Research Fellow at Royal College of Physicians. No mention of COI.
Sample Size	N = 306 patients with a first seizure occurrence.
Age/Sex	No mention of mean age, age range: 16–80 or more years. 182 males, 124 females.
Comparison	Study Group: Patients were evaluated on family history, biographical details, and seizure description, then 95% of patients were given an EEG and 92% of patients were given CT and were followed to note the occurrence of any recurrent seizures.
Follow-Up	Follow-up at 3 and 6 months then at 1, 2, and 3 years.
Results	There is a significantly higher rate of seizure recurrence for patients seen within 8 weeks of their first seizure versus after. By the end of 3 years, 52% of patients seen within 1 week of their seizure had a recurrent seizure. There was a significant difference in the risk of recurrent seizures for patients whose first seizure happened between midnight and breakfast vs. any other time (p < 0.003). There was a significant difference in recurrent seizure risk for patients whose CT showed a tumor vs. those without a tumor.
Conclusion	"First seizures cause considerable personal and family distress. The principal role of a neurologist should be to examine, to explain, to advise, and to reassure. Electroencephalography is not necessary, nor is CT scanning except in the circumstances we have defined."

Comments	Longitudinal case series. Dropouts unclear. Increased risk of recurrence with non-significant increasing risks of younger age, family history.

Author, Year Score: 6*	Hauser, 1998, Epilepsia; Unprovoked; Untreated Title: Risk of recurrent seizures after two unprovoked seizures. Seizure Types: Unprovoked seizures.
Category	Seizure
Study Type	Retrospective longitudinal case series
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 204 patients with a single unprovoked seizure.
Age/Sex	Mean age: 36 years. 142 males, 62 females.
Comparison	Study Group: Patients were followed prospectively to classify the seizure as partial or generalized and idiopathic or cryptogenic or remote symptomatic then followed to analyze the occurrence and circumstances of any recurrent seizures to evaluate the risk of recurrent seizures by Kaplan-Meier method (n = 204).
Follow-Up	Follow-up twice a year for 2 years, then annually indefinitely.
Results	There was a 33% risk of a second unprovoked seizure, a 73% risk of a third unprovoked seizure based on those with a second, and a 76% chance of a fourth unprovoked seizure of those who had a third. Relative risk (95% CI) of a third seizure for those with a presumed cause of epilepsy: 1.9 (1.0, 3.4).
Conclusion	"Although only about one third of patients with a first unprovoked seizure will have further seizures within five years, about three quarters of those with two or three unprovoked seizures have further seizures within four years."
Comments	Retrospective longitudinal case series. Low dropouts. Most treated with antiepileptic drugs.

Author, Year Score: 4.5	First Seizure Trial Group, 1993, Neurology; Unprovoked; Treated Title: Randomized clinical trial on the efficacy of antiepileptic drugs in reducing the risk of relapse after a first unprovoked tonic-clonic seizure. Seizure Types: Unprovoked tonic-clonic seizures.
Category	Seizure
Study Type	RCT
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 397 patients with a single seizure occurrence.
Age/Sex	No mention of mean age, age range: 2–70 years. 229 males, 168 females.
Comparison	Treatment Group: Patients immediately received monotherapy with 4 to 10 µg/ml carbamazepine (CBZ), 110 to 20 µg/ml phenytoin (PHT), 15 to 40 µg/ml phenobarbital (PB) or 50 to 100 µg/ml sodium valproate (SV) based on their doctor's preference (n = 204) vs. Recurrent Treatment Group: Patients received one of the drug treatments above only after a recurrent seizure (n = 193).
Follow-Up	Follow up at 1, 3, and 6 months, then every 6 months indefinitely.
Results	The proportion (percent) of patients with recurrent seizure in Treatment vs. Recurrent Treatment Group: 36/204 (18%) vs. 75/193 (39%). The cumulative time-dependent risk of relapse for Treatment vs. Recurrent Treatment Group after 1 year: 25% vs. 51%. The risk of relapse (95% CI) was 2.8 (1.9, 4.2) times higher for Recurrent Treatment vs. Treatment Group.

Conclusion	"[C]ontrary to previous observational studies and in keeping with the other randomized trial, we demonstrated that treatment with antiepileptic drugs leads to a significant reduction of the risk of seizure recurrence after a first unprovoked seizure. The decision to start the treatment in a patient with a first seizure must therefore rely on a balance between his or her risk of relapse, the benefits of avoiding the consequences of a second seizure, and the risk of antiepileptic drugs toxicity."
Comments	RCT of immediate recurrence. Delayed treatment after first tonic-clonic seizure. Untreated with more Family history of seizures. 20% stopped antiepileptic drugs. Younger have higher risk of recurrence. Data show 50% reduction in recurrence 2 years.

Author, Year Score: 6*	Hesdorffer, 2009, Epilepsia; Unprovoked; Untreated Title: Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. Seizure Types: Generalized seizures including generalized tonic, clonic, and tonic-clonic seizures.
Category	Seizure
Study Type	Population study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 410 individuals who had experienced either a first acute symptomatic seizure or first unprovoked seizure from 1955–1984 (262 symptomatic and 148 unprovoked).
Age/Sex	No mention of mean age. Age ranges: 24 participants < 1 years of age, 110 between ages 1–19, 121 between ages 20–64, and 155 > 65 years. 229 males, 181 females.
Comparison	Group 1: Participants who had experienced a first acute symptomatic seizure were observed for short-term mortality probability over 30 days and for long-term mortality probability plus risk of subsequent unprovoked seizures throughout 10 years (n = 262) vs. Group 2: Participants who had experienced a first unprovoked seizure were observed for same factors and time span as Group 1 (n = 148).
Follow-Up	Follow-up over span of 10 years.
Results	With respect to short-term mortality, Group 1 cumulative mortality probability was much higher at 21.4% (95% CI: 16.9%–26.9%) vs. Group 2 at 3.4% (95% CI: 1.4%–7.9%, $p < 0.001$). Over 10-year span, Group 2 had higher mortality probability and risk of subsequent unprovoked seizures at 54.9% (46.2%–64.0%) and 64.8% (55.1%–74.4%) respectively vs. Group 1 at 33.4% (26.3%–41.7%) ($p < 0.001$) and 18.7% (13.7%–25.4%) ($p < 0.001$).
Conclusion	"The prognosis of first acute symptomatic seizures differs from that of first unprovoked seizure when the etiology is stroke, TBI, and CNS infection. Acute symptomatic seizures have a higher early mortality and a lower risk for subsequent unprovoked seizure. These differences argue against the inclusion of acute symptomatic seizures as epilepsy."
Comments	"Static brain lesions" includes stroke, TBI, CNS infection. Much higher risk if unprovoked if acute symptomatic seizure.

Author, Year Score: 5	Haltiner, 1997, Archs Phys Med Rehabil; Unprovoked; Treated Title: Risk of seizure recurrence after the first late posttraumatic seizure. Seizure Types: Mention of late posttraumatic seizures.
Category	Prophylaxis using phenytoin
Study Type	Longitudinal case series study
Conflict of Interest	Sponsored by the National Institutes of Neurologic Disorders and Stroke, the National Center for Medical Rehabilitation Research, and the Agency for Health Care Policy and Research. No mention of COI.
Sample Size	N = 63 patients with moderate to severe head injuries who developed late posttraumatic seizures during an RCT for prophylactic treatment of posttraumatic seizures using phenytoin.
Age/Sex	Mean age: 31 years ± 15. 50 males, 13 females.
Comparison	Only one group was analyzed for this study.
Follow-Up	Follow-up duration: Median of 730 days from initial injury and 488 days from the initial late seizure.
Results	Out of the 63 patients selected, 8 died, and 5 dropped out before the 2-year mark. Risk of seizure recurrence was 47% in 1 month. Incidence of recurrence was 69% at 6 months, 82% at 1 year, and about 86% at 2 years. In the first 2 years after the initial late seizure (7 days after head injury), 52% had a minimum of 5 late seizures, 37% had a minimum of 10 seizures. Patients with only one seizure were less likely to have an acute subdural hematoma when compared to individuals with a minimum of two seizures (chi-squared = 6.4, $p = 0.01$). According to the Glasgow Coma Scale, people with a score of 3 to 5 had a risk ratio of 3.05 ($p = 0.05$) for 5 or more seizures. Individuals with a coma lasting longer than 7 days had risk ratios of 4.45 ($p = 0.02$) for 5 or more seizures and 7.67 ($p = 0.05$) for 10 or more seizures.
Conclusion	"When late seizures develop after severe head injury, the probability of recurrence is high, which suggests that patients be treated aggressively with anticonvulsant medication after a first unprovoked late seizure."
Comments	Sub-study of RCT. Longitudinal case series. Data suggest high recurrence after first late seizure. Some risks and correlated with TBI severity measures.

Author, Year Score: 6*	Hui, 2001, Epilepsia; Unprovoked, Untreated Title: Recurrence after a first untreated seizure in Hong Kong Chinese population. Seizure Types: Tonic-clonic seizures.
Category	Recurrence after first untreated seizure
Study Type	Retrospective study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 132 patients with a witnessed, unprovoked generalized tonic-clonic seizure whose medications were withheld.
Age/Sex	Mean age: 33 years. 66 males, 66 females.
Comparison	Statistics were conducted within the group under consideration.
Follow-Up	Mean duration of Follow up: 27.2 months Follow up duration:(n = 87) 1 year, (n = 77) 2 years, (n = 49) 3 years, (n = 21) 4 years.

Results	Mean Time between seizure and electroencephalogram: 15.7 days. 64% of patients had CT scans. 6.8% had brain abnormalities defined as cerebral atrophy, arachnoid cysts, or subclinical cerebrovascular disease. Recurrence risk was found to be: 30% for 1 year, 37% for 2 years, 42% for 3 years, 47% for 4 years. Multivariate Analysis with Cox regression model factors were as follows: Abnormal CT scan (risk ratio 2.44, 95% CI 1.09–5.44, $p < 0.03$), other potential risk factors and nocturnal seizures (risk ratio 0.61, 95% CI 0.3–1.25, $p = 0.18$). See Table .
Conclusion	"Thirty percent of the sample population experienced a second seizure after 1 year. An additional 17% continue to be at risk of a second convulsion during the next 3 years."
Comments	Retrospective longitudinal case series. Dropouts unclear. First unprovoked and untreated.

Author, Year Score: 6*	Hauser, 1990, Epilepsia; Unprovoked; Untreated Title: Seizure recurrence after a 1st unprovoked seizure: An extended follow-up. Seizure Types: Idiopathic, remote symptomatic as defined by the study.
Category	Predictor identification for seizure recurrence after first unprovoked seizure
Study Type	Longitudinal case series study
Conflict of Interest	Supported by NS 1308-11. No mention of COI.
Sample Size	N = 208 patients with 1 unprovoked seizure.
Age/Sex	Not listed.
Comparison	Statistics were conducted within the group under consideration. No between group comparisons made with statistical analysis.
Follow-Up	Follow-up period: 4 years. Patients were contacted every 6 months for the first 2 years after which they were contacted once each year.
Results	Multivariate analysis via Cox regression analysis for the total group yielded these significant variables: Etiology (rate ratio: 2.55, 95% CI: 1.44–4.51, $p \leq 0.05$), Todd's paresis (rate ratio: 1.94, 95% CI: 1.18–4.51, $p \leq 0.05$), Sibling affected (rate ratio: 1.99, 95% CI: 1.09–3.60, $p \leq 0.05$), Prior acute seizures (rate ratio: 2.69, 95% CI: 1.56–4.62, $p \leq 0.01$), generalized spike-wave (GSW) EEG pattern (rate ratio: 2.16, 95% CI: 1.07–4.38, $p \leq 0.05$). For the idiopathic group (n = 149) only Sibling affected (rate ratio: 2.51, 95% CI: 1.23–5.11, $p \leq 0.05$), and GSW EEG pattern (rate ratio: 2.69, 95% CI: 1.28–5.67, $p \leq 0.05$) were significant predictors. For the remote group, only Todd's paresis (rate ratio: 2.93, 95% CI: 1.31–6.54, $p \leq 0.01$) and Prior acute seizures (rate ratio: 4.75, 95% CI: 1.82–12.42, $p \leq 0.01$) were significant predictors. Estimated risk of recurrence at: 1 year was 14%, 3 years was 29%, and 5 years was 34%.
Conclusion	"Although no studies published heretofore have been designed specifically to evaluate [anticonvulsant medication (AED)] therapy, some analyses of the factor have invariably been attempted. No study has shown treatment to reduce recurrence risks, and in some, such as the present study, prescription of AED was associated with an increased recurrence risk even when controlling for other risk factors. ...In general, patients in the present study given AED were placed on low dosages, levels were not monitored or adjusted, and many did not take the medication on a regular basis if at all. The question of AED effect can only be addressed in a randomized clinical trial with careful monitoring of AED use in treated patients."
Comments	Longitudinal case series. Low dropouts.

Author, Year Score: 4*	Punia, 2015, Epilepsy Behav; Unprovoked/Epilepsy; Untreated Title: Incidence of recurrent seizures following hospital discharge in patients with LPDs (PLEDs) and nonconvulsive seizures recorded on continuous EEG in the critical care setting. Seizure Types: Nonconvulsive seizures.
Category	Seizure reoccurrence in patients with nonconvulsive seizures (NCS) and periodic lateralized epileptiform discharges (PLEDs)
Study Type	Retrospective case series study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 118 patients that had PLED and/or NCS as diagnosed by continuous electroencephalography (cEEG) in 2013.
Age/Sex	Mean age: 60.7 years ± 18.3. 56 males, 62 females.
Comparison	PLEDs + Seizure (n = 51), PLEDs only (n = 45), seizure only (n = 22).
Follow-Up	Mean follow-up: 11.9 months ± 6.
Results	46.6% of overall patients had recurring seizures. This was significantly different between the groups ($p < 0.001$). 24% in the PLEDs only had reoccurring seizures. Patients with NCS w/ or w/o PLEDS were more likely to have reoccurring seizures (OR 4.97 (2.17–11.4), $p < 0.001$). These patients had a ≥ chance of being on antiepileptic drugs. (OR 4.92 (1.4–16.8), $p = 0.006$). 100% of tumors were associated with the PLEDS diagnosis (OR 0.36 (0.1–1.05), $p = 0.09$). No significant difference between the groups was found in relation to ischemic stroke or hemorrhage ($p \geq 0.05$). PLED diagnosis had significantly more focal lesions when compared to the seizure only group (OR 10.25 (3.63–28. 91), $p < 0.001$).
Conclusion	"Our study found a very high rate of post-hospital discharge seizures in the patients who had PLEDs and/or NCS while on cEEG in the ICU. We report for the first time in the literature that a significant percentage of patients with only PLEDs and no ICU seizures develop de novo seizures after hospital discharge. The risk of seizures post discharge shows a steep jump if PLEDs are accompanied by NCS at the time of acute brain injury. One worrisome finding is the high rehospitalization rate in this patient population. Future prospective studies need to be undertaken to further shed light on the findings reported in our study."
Comments	Retrospective longitudinal consecutive case series. Author comment on some generalizability issues. Quite limited to database inclusion criteria with cEEG monitoring following hospital discharge. Data suggest 17% without seizure history had seizures after discharge if PLEDs and 60% if had seizures. Dropouts unclear.

Author, Year Score: 5	Kim, 2006, Lancet Neurol; Epilepsy/Unprovoked; Treated Title: Prediction of risk of seizure recurrence after a single seizure and early epilepsy: Further results from the MESS trial. Seizure Types: All types of seizures.
Category	Seizure reoccurrence with immediate treatment of antiepileptic drugs
Study Type	RCT
Conflict of Interest	Sponsored by UK Medical Research Council and Raymond and Beverly Sackler Studentship Award. No mention of COI.
Sample Size	N = 1,443 people who had at least one recent epileptic seizure.
Age/Sex	Mean age: 31.2 years. 815 males, 628 females.

Comparison	People who had a seizure and immediately started taking drugs to treat it (n = 866) vs. people who had a delayed treatment until their doctor deemed that they were fit to take antiepileptic drugs (n = 577).
Follow-Up	Follow-up after 3, 6, and 12 months.
Results	People with low risk had a prognostic index of ≤ 0.3, medium risk had a prognostic index of 0.3–0.49 and high risk had a prognostic index of ≥ 0.5. No noticeable difference between low-risk people, but medium and high-risk people had great improvements. (p = 0.008)
Conclusion	"The model shows that there is little benefit to immediate treatment in patients at low risk of seizure recurrence, but potentially worthwhile benefits are seen in those at medium and high risk."
Comments	Large case series. Data suggest antiepileptic drug treatment after one seizure of little benefit.

Author, Year Score: 5*	Hart, 1990, Lancet; Unprovoked; Untreated Title: National general practices study of epilepsy: Recurrence after a first seizure. Seizure Types: Not specified.
Category	Seizure
Study Type	Longitudinal case series study
Conflict of Interest	Sponsored by Brain Research Trust, the National Fund for Crippling Diseases, the British Epilepsy Research Foundation, and the National Society for Epilepsy. No mention of COI.
Sample Size	N = 564 people who have been identified to have definite epileptic seizure.
Age/Sex	Age: 164 below 15, 180 between 16–39, 93 between 40–59, and 127 aged 60 or older. No mention of sex.
Comparison	(N = 564) patients followed for 2–4 years to observe their risk of recurrence for seizures. (N = 460) were followed up for the entire 2–4 years, (n = 67) died, and (n = 37) were lost to follow-ups.
Follow-Up	Follow-up after 6 months.
Results	Risk for seizure recurrence fell with the amount of time someone went seizure-free. Recurrence was 44% (33–55%) after being seizure-free for 6 months; 32% (18–46%) for being seizure-free for 12 months; and 17% (0–35%) for being seizure-free for 18 months. Only 15% of patients were treated after their first seizure. Recurrence was lower in the treated group: 38% (27–48%) by 6 months; 50% (40–61%) by 12 months; and 57% (46–68%) by 36 months vs. the untreated group: 64% (60–69%) by 6 months; 70% (66–74%) by 12 months; and 81 (77–85%) by 36 months.
Conclusion	"Traditionally, a single seizure is not considered to be epilepsy, which is often defined by the occurrence of two or more attacks. Since the recurrence rate after a single seizure is so high, we wonder whether this arbitrary distinction between single seizures and epilepsy has any value. If it is meaningful in an individual, it is only so when the time elapsed from the first attack is known."
Comments	Data suggest risk is bi-modal or "U" shaped.

Author, Year Score: N/A	Aktekin, 2006, Epilepsy Behav; Unprovoked/Epilepsy; Untreated Title: Withdrawal of antiepileptic drugs in adult patients free of seizures for 4 years: A prospective study. Seizure Types: Epilepsy.
Category	Seizure, antiepileptic drugs
Study Type	Interventional Tapering study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 49 patients with epilepsy with 2 unprovoked seizures 24 hours apart who were seizure-free for at least 4 years.
Age/Sex	Mean age: 38.98 years. 22 males, 27 females.
Comparison	Patients who relapsed while withdrawing from antiepileptic medications (n = 28) vs. patients who did not relapse after withdrawing from antiepileptic medications (n = 21).
Follow-Up	There was a mean follow-up time of 37.2 months.
Results	Relapse probabilities for tapering period was 21.4%, 28.6% for 1 month, 14.3% for 3 months, 3.6% for 6 months, 7.1% for 12 months, and 17.8% for 24 months. A logistic regression model was not able to be adapted for this study ($p > 0.05$). The two major risks for recurrence were age at the onset of epilepsy and duration of active disease ($p < 0.05$, Student t test).
Conclusion	"The aim of this prospective study was to identify the risk factors for seizure recurrence during and/or after slow withdrawal of antiepileptic drugs in an adult patient population. However, this study has several limitations. First, the number of patients was small; therefore, some potential risk factors such as symptomatic etiology could not be assessed precisely. Second, based on the patients' willingness, we stopped or continued the withdrawal even during the tapering period, which also may have influenced our results. Third, we excluded patients who had unsuccessfully attempted drug withdrawal twice before."
Comments	Small study of 49. Data suggest age at onset and duration were recurrence risks.

Author, Year Score: 4*	Van Donselaar, 1992, Arch Neurol; Unprovoked; Untreated Title: Value of the electroencephalogram in adult patients with untreated idiopathic first seizures. Seizure Types: Sleep epilepsy.
Category	Seizure, idiopathic seizures
Study Type	Prospective study
Conflict of Interest	Sponsored by TNO Research Committee on Epilepsy of the Division of Health Research TNO. No mention of COI.
Sample Size	N = 157 patients with untreated idiopathic first seizures.
Age/Sex	Mean age: 38 years. 93 males, 64 females.
Comparison	All 157 patients had an EEG used on them to predict the risk of recurrence and EEG was used when the patients experienced sleep deprivation.
Follow-Up	Follow-up after 2 years.
Results	Epileptic discharges were associated with risk of recurrence for 83% of patients (95% CI, 69–97%) vs. 41% for those with nonepileptic abnormalities (95% CI, 29–53%). Finally, 12% who had normal EEG (95% CI, 3– 21%).

Conclusion	"The moderate reliability of visual EEG interpretation certainly requires improvements and makes extrapolation of our findings hazardous. The good predictive value for all four observers despite the considerable interobserver variation, however, illustrates that the EEG is a potentially accurate instrument to predict risk of recurrence."
Comments	Study of EEG utility.

*Study design may be reclassified, especially from "cohort" to "longitudinal case series study" for those studies consisting of a series of patients followed longitudinally.

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APPENDIX B: SEIZURE RECURRENCE RISK AFTER FIRST PROVOKED SEIZURE, WITH AND WITHOUT ANTIEPILEPTIC DRUG TREATMENT

There are no quality studies to answer this key question regarding provoked seizures.

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APPENDIX C: SEIZURE RECURRENCE RISK AFTER STROKE, WITH AND WITHOUT ANTIEPILEPTIC DRUG TREATMENT

Author, Year Score: N/A	Devinsky, 1983, Neurology; Provoked; Untreated Title: Seizures after convulsive therapy: A retrospective case survey. Seizure Types: Spontaneous seizures.
Category	Convulsive therapy
Study Type	Retrospective longitudinal case Series
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 81 patients without precursor seizure conditions and had recorded spontaneous seizures following convulsive therapy.
Age/Sex	Mean age: 32.5 years. 49 males, 32 females.
Comparison	This study analyzed the different convulsive modalities in patients being treated for spontaneous seizures. The different modalities were electroconvulsive shock therapy (ECT) applied with bilateral electrode placement (n = 29), pentylenetetrazol applied with bilateral electrode placement (n = 22), insulin (n = 2), and multiple (n = 28).
Follow-Up	Follow-up between 3 months to 25 years.
Results	There was a calculated annual average incidence of new onset seizures of 114 per 100,000 after ECT, which is 5 times greater than the incidence found in the non-psychiatric population.
Conclusion	"Host susceptibility rather than treatment features influenced seizure development. A longer latency to first seizure was associated with greater likelihood of seizure recurrence, a relationship also observed in posttraumatic epilepsy."
Comments	Retrospective longitudinal case series. Data suggest variable and unpredictable risks and many recurrences.

Author, Year Score: N/A	Kho, 2006, Neurology; Provoked/Unprovoked; Treated/Untreated Title: First seizure presentation: Do multiple seizures within 24 hours predict recurrence? Seizure Types: No seizure type specified.
Category	Seizure
Study Type	Longitudinal case series
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 497 patients with a first seizure occurrence.
Age/Sex	Mean age: 40.5 years. 322 males, 175 females.
Comparison	Study Group: Patients with two or more seizures separated by a recovery period within 24 hours (n = 72) vs. Comparison Group: Patients with a single seizure (n = 425). 97% of all patients received an EEG and 95% received neuroimaging.
Follow-Up	Follow-up at 12 months.

Results	Number (percent) of patients with generalized tonic-clonic seizures in Study vs. Comparison Group: 64 (96%) vs. 408 (96%). Prediction of multiple seizures based on odds ratio for older age (95% CI): 1.02 (1.01, 1.03), (p = 0.005) and based on provoked etiology: 1.88 (1.08, 3.22), (p = 0.02). Mean Age (years) for Study Group vs. Comparison Group: 43 vs. 38 (p = 0.01). Number (percent) of provoked seizures for Study vs. Comparison Group: 26 (36%) vs. 111 (26%), (p = 0.05). Number (percent) of Focal for Study vs. Comparison Group: 13 (19%) vs. 33 (8%), (p = 0.007). Number (percent) patients treated after first seizure for Study vs. Comparison Group: 38 (53%) vs. 89 (21%), (p < 0.001).
Conclusion	"Overall, treated patients had a higher seizure recurrence rate, irrespective of whether they were in the single- or multiple-seizure groups. This is consistent with the strong correlation of factors influencing the decision to start treatment and factors predictive of recurrence, including remote symptomatic etiology."
Comments	Case-control study. Multiple seizures within 24 hours. found unlikely to predict recurrence. As to 45-55-year-olds treated with antiepileptic drugs, conclusions tentative.

Author, Year Score: 2.5	Chadwick, 1996, Epilepsia; Provoked/Unprovoked; Treated Title: Outcomes after seizure recurrence in people with well-controlled epilepsy and the factors that influence it. Seizure Types: All types.
Category	Medications, seizure
Study Type	Longitudinal case series study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 409 patients with recurrent seizures.
Age/Sex	No mention of age or sex.
Comparison	Patients were placed on antiepileptic drugs and were monitored for 6 months to see how often recurrences occurred. If patients were to die the study would cease from following that patient, but still include them.
Follow-Up	Follow-up after 6 months, 1 year, and 2 years.
Results	Of all the patients 51% of them were able to remain seizure-free (95% confidence limits 45, 56%) within the first year and 40% within 2 years (95% confidence limits 35, 45).
Conclusion	"Our results provide no evidence that discontinuation of antiepileptic drugs modifies the long-term prognosis of a person's epilepsy, although it does increase the risk of seizures in the 1- to 2-year period after discontinuation."
Comments	Data suggest increased seizures after antiepileptic drugs discontinuation.

Author, Year Score: 4*	Kim, 2016, BMC Neurol; Provoked/Epilepsy; Treated Title: Clinical predictors of seizure recurrence after the first post-ischemic stroke seizure. Seizure Types: Post-ischemic stroke seizures (specific type not mentioned).
Category	Seizure
Study Type	Observational study

Conflict of Interest	Sponsored by grants from Korea Health Technology R&D Project via Korea Health Industry Development Institute and funding from Ministry of Health and Welfare and Basic Science Research Program via the National Research Foundation of Korea. No COI.
Sample Size	N = 124 patients who had experienced post-stroke seizure after ischemic stroke (PSSi).
Age/Sex	Mean age: 66.3 years. 69 males, 55 females.
Comparison	Group 1: Patients with early onset PSSi, or onset PSSi within 7 days from stroke onset (n = 48) vs. Group 2: Participants with late onset PSSi, or onset past 7 days of stroke onset (n = 76).
Follow-Up	Follow-up varying with a mean of 44.4 months.
Results	With reference to seizure recurrence, Group 1 experienced 35.4% vs. Group 2 at 48.7%. With reference to factors associated with seizure recurrence, these included atrial fibrillation ($p = 0.016$) and large/cortical stroke lesions ($p < 0.05$) being more common in Group 2 vs. Group 1. Common factors for recurrence for Group 2 were young age, gender (more likely in males), and large lesions vs. Group 1 with factors being gender (again male), atrial fibrillation, and lesions.
Conclusion	"Our study characterized the high-risk group for seizure recurrence in patients with the first PSSi. PSSi patients with high-risk score of seizure recurrence had a greater chance of developing epilepsy later. Therefore, they should be considered for further treatment such as antiepileptic drug medication in clinical practice."
Comments	Retrospective longitudinal case series. Registry based, post-stroke study.

Author, Year Score: 3*	Berges, 2000, Eur Neurol; Unprovoked; Untreated Title: Seizures and epilepsy following strokes: Recurrence factors. Seizure Types: Poststroke seizures, early onset, and late onset.
Category	Identification of factors and rates associated with reoccurring seizures in stroke patients
Study Type	Retrospective case series study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 159 patients with first ischemic stroke, and primary intracerebral hemorrhage.
Age/Sex	Mean age: 67.1 years ± 15.2. 96 males, 63 females.
Comparison	Statistics were conducted within the group under consideration. No between group comparisons made with statistical analysis.
Follow-Up	Mean follow-up period 47 months.
Results	53 patients had early onset of seizures, 4 had premonitory and 102 had late onset seizures in relation to time of first stroke. Lesion locations is as follows: cortical 87.4%, frontal 42.7%, temporal 32.7%, parietal 27.7, occipital 11.9%, parietotemporal-occipital 8.2%, subcortical 3.8%, and infratentorial 1.3%. Poststroke seizure reoccurrence is 17.8% of patients experiencing a single, and 32.6% experiencing multiple. Multivariate analysis with logistic regression yielded two predictive factors: occipital lesion (relative risk: 7.68, 95% CI: 1.00–83.8) and late-onset seizures (relative risk: 3.89, 95% CI: 1.00–15.5).
Conclusion	"This study confirms that poststroke seizures are frequent and must be divided into 2 types: early-onset (within 14 days) and late-onset seizures. It demonstrates that a significantly lower rate of patients with early-onset seizures develop another seizure, i.e., epilepsy, than do patients with late-onset seizures. Other factors are involved in recurrence suggesting that poststroke epilepsy probably occurs in a chronically injured brain. The problem of treatment remains unanswered."

Comments	Retrospective longitudinal case series.

Author, Year Score: 1*	Tomari, 2017, Seizure; Unprovoked; Untreated Title: Risk factors for post-stroke seizure recurrence after the first episode. Seizure Types: Acute symptomatic and unprovoked (first episode) seizures (specific type not mentioned).
Category	Seizure
Study Type	Observational study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 153 patients who had experienced the first episode of post-stroke seizure (PSS) between July 2010 and June 2014.
Age/Sex	Mean age: 73.7 years. 84 males, 69 females.
Comparison	Group 1: Patients who had PSS within 1 week after their stroke (ES or early seizures) (n = 63) vs. Group 2: Patients who had PSS the second week or later after having had a stroke (LS or late seizures) (n = 90).
Follow-Up	Follow-up median of 364 days (IQR 124–680 days) for 113 patients.
Results	Factor of mortality was higher in Group 1 than in Group 2, and seizure recurrence was lower in Group 2 (shown graphically, no statistics included). Using the Cox proportional hazards model for the identification of predictors of seizure recurrence (where a ratio less than 1 is a hazard reduction and above is an increase), age and status epilepticus had hazard ratios of 0.95 (95% CI: 0.93–0.99, younger is higher in hazard, $p > 0.05$) and 4.75 (95% CI: 1.28–17.62, $p > 0.05$) respectively.
Conclusion	"In patients with a first episode of PSS, late onset of seizure significantly increased the rate of recurrence when compared to early onset seizure. The independent predictors of seizure recurrence after the first episode of PSS were status epilepticus for ES and young age for LS."
Comments	Retrospective longitudinal case series. High dropouts in late seizure group.

Author, Year Score: 6*	Kotsopoulos, 2005, Seizure; Epilepsy/Unprovoked Title: Incidence of epilepsy and predictive factors of epileptic and non-epileptic seizures. Seizure Types: Not specified.
Category	Seizure, epilepsy
Study Type	Prospective population-based study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 268 patients with a first seizure or who had undiagnosed seizures.
Age/Sex	Age range: 40 between 14–24, 45 between 25–44, 86 between 45–64, and 97 aged 65 or older. 137 males, 131 females.
Comparison	Patients who were experiencing epilepsy (n = 94) vs. patients who were experiencing a first unprovoked seizure (n = 174).
Follow-Up	Follow-up after 6 months
Results	For those patients with unprovoked seizures, 45.7% had a n index seizure, 17.9% had more than 5 recurrent seizures. The kappa value for the inter-rater agreement gave good results (0.92, 95% CI: 0.88–0.96).

Conclusion	"Non-epileptic seizures are often misdiagnosed as epileptic seizures. Obviously, in case of a single seizure, the potential of misdiagnosis is increased. The predictive factors found in this study may assist clinicians in the diagnosis of seizures. Hence, based on certain issues such as findings from diagnostic tests (CT or EEG), they may distinguish patients with epileptic seizures from patients with non-epileptic seizures."
Comments	Data suggest risk factors for seizures include EEG, hypertension, cardiovascular disease, head injury, and female sex.

Author, Year Score: 2*	Park, 1998, Seizure; Unprovoked; Treated Title: Clinical courses of pure sleep epilepsies. Seizure Types: Not specified.
Category	Seizure, sleep epilepsy
Study Type	Retrospective review
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 42 patients with pure sleep epilepsy.
Age/Sex	Mean age: 18.4 years, no other age information provided. 21 males, 21 females.
Comparison	Patients who experienced a recurrence in seizures (n = 27) vs. patients who are seizure-free (n = 15).
Follow-Up	Follow-up after 2 years.
Results	Mean age of onset did not differ between those who were newly diagnosed or not to sleep epilepsy ($p = 0.03$). The baseline seizure frequency was higher ($p = 0.02$). Incidence of wake seizures was higher in those who had some form of head trauma ($p = 0.06$).
Conclusion	"We conclude that a thorough evaluation of the patients with S-PE is crucial for predicting their future clinical course. Patients with [generalized tonic-clonic seizure during sleep (S-GTCS)] without any focal features in seizure phenomenology, EEG, and neuroimaging studies easily enter a prolonged seizure remission and the risk of developing WS is quite low. With respect to the GTCS on awakening criterion, some of these patients (especially those having infrequent attacks) may have idiopathic S-GTCS."
Comments	Data suggest seizures while awake are common among those with sleep epilepsies.

*Study design may be reclassified, especially from "cohort" to "longitudinal case series study" for those studies consisting of a series of patients followed longitudinally.

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APPENDIX D: SEIZURE RECURRENCE RISK AFTER DIAGNOSIS OF EPILEPSY, WITH AND WITHOUT ANTIEPILEPTIC DRUG TREATMENT

Author, Year Score: 2*	Tanaka, 1992, Jpn J Psychiatry Neurol; Epilepsy; Treated Title: Long-term effectiveness of antiepileptic drug treatment and seizure recurrence in patients with epilepsy. Seizure Types: Not listed; epileptic classifications include idiopathic generalized epilepsy, symptomatic generalized epilepsy, temporal lobe epilepsy, partial epilepsy other than the temporal lobe form, and other epilepsies.
Category	Antiepileptic drug therapy
Study Type	Retrospective study
Conflict of Interest	Sponsored by the Aichi Health Promotion Foundation. No mention of COI.
Sample Size	N = 334 patients with seizures controlled by antiepileptic drugs for 3 years.
Age/Sex	Mean age: 37.4 years range 20–65 years, no other age information provided. 164 males, 170 females.
Comparison	Statistics were conducted within the group under consideration.
Follow-Up	Follow-up occurred over a period from April 1988 to March 1991.
Results	Of the total, 36.5% of patients were seizure-less from April 1985 to March 1988 (observation period), while 51.2% experienced one or more seizures. 12.3% experienced seizures during this period due to withdrawal of antiepileptic drug therapy. 48.8% of patients were considered "seizure-free." Of the "seizure-free" patients, 90.8% remained so from April 1988 to March 1991(follow-up period), while 9.2% had one or more seizures. Of patients who experienced seizures, 78.4% experienced one or more seizures. For this group, the seizure rate increased significantly ($p < 0.01$) for patients who had a seizure closer to the beginning of the follow-up period. Overall, significantly more patients without reoccurring seizures received antiepileptic drug treatment when compared to patients with reoccurring seizures ($p < 0.05$).
Conclusion	"Enabling patients with epilepsy to remain seizure-free for at least three years because of antiepileptic drug treatment and ensuring good compliance can reduce the seizure recurrence rate to less than 10%. We believe that our findings on the long-term effectiveness of antiepileptic drugs and their influence on the seizure recurrence rate will be useful in furthering legal debate over the problem of allowing patients with epilepsy to obtain driving licenses."
Comments	Study of seizure risk over time in a retrospective case series.

Author, Year Score: 5*	Lossius, 1999, Seizure; Epilepsy; Untreated Title: Predictors for recurrence of epileptic seizures in a general epilepsy population. Seizure Types: Epileptic seizures.
Category	Predictor identification for epileptic seizure recurrence
Study Type	Retrospective study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 669 patients with epilepsy defined by ICD 9 code 345.
Age/Sex	Mean age: 44 years ± 12, no other age information provided. 338 males, 331 females.

Comparison	Statistics were conducted within the group under consideration.
Follow-Up	No follow up mentioned.
Results	Univariate logical regression analysis yielded two predictors: age > 50 (Odds ratio: 1.6, 95% CI: 1.1–2.2, p = 0.02), and individuals who had taken 2 or more antiepileptic drugs (Odds ratio: 4.6, 95% CI: 0.5–1.2, p < 0.001). Multivariate analysis yielded the same two predictors: age (Odds ratio: 1.7, 95% CI: 1.1–2.6, p = 0.0216), and 2 or more antiepileptic drugs (Odds ratio: 5.6, 95% CI: 2.7–11.9, p < 0.0001).
Conclusion	"In conclusion, we found that age above 50 years and the use of two or more antiepileptic drugs were predictors for recurrence of seizures in a general epilepsy population. Our study demonstrates some of the difficulties in identifying reliable predictors for recurrence of epileptic seizures retrospectively."
Comments	Retrospective longitudinal case series. Dropouts unknown.

Author, Year Score: 4*	Punia, 2015, Epilepsy Behav; Epilepsy/Unprovoked, Untreated Title: Incidence of recurrent seizures following hospital discharge in patients with LPDs (PLEDs) and nonconvulsive seizures recorded on continuous EEG in the critical care setting. Seizure Types: Nonconvulsive seizures.
Category	Seizure reoccurrence in patients with nonconvulsive seizures (NCS) and periodic lateralized epileptiform discharges (PLEDs)
Study Type	Retrospective Case Series Study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 118 patients that had PLED and/or NCS as diagnosed by cEEG in 2013.
Age/Sex	Mean age: 60.7 years ± 18.3, no other age information provided. 56 males, 62 females.
Comparison	PLEDs + Seizure (n = 51), PLEDS only (n = 45), seizure only (n = 22).
Follow-Up	Mean follow-up: 11.9 months ± 6.
Results	46.6% of overall patients had recurring seizures. This was significantly different between the groups (p < 0.001). 24% in the PLEDs only had reoccurring seizures. Patients with NCS with or without PLEDS were more likely to have reoccurring seizures (OR 4.97 (2.17–11.4), p < 0.001). These patients had a ≥ chance of being on antiepileptic drugs (OR 4.92 (1.4–16.8), p = 0.006). 100% of tumors were associated with the PLEDS diagnosis (OR 0.36 (0.1–1.05), p = 0.09). No significant difference between the groups was found in relation to ischemic stroke or hemorrhage (p ≥ 0.05). PLED diagnosis had significantly more focal lesions when compared to the seizure only group (OR 10.25 (3.63–28. 91), p < 0.001).
Conclusion	"Our study found a very high rate of post-hospital discharge seizures in the patients who had PLEDs and/or NCS while on cEEG in the ICU. We report for the first time in the literature that a significant percentage of patients with only PLEDs and no ICU seizures develop de novo seizures after hospital discharge. The risk of seizures post discharge shows a steep jump if PLEDs are accompanied by NCS at the time of acute brain injury. One worrisome finding is the high rehospitalization rate in this patient population. Future prospective studies need to be undertaken to further shed light on the findings reported in our study."
Comments	Retrospective longitudinal consecutive case series. Author comment on some generalizability issues. Quite limited to database inclusion criteria with cEEG monitoring following hospital discharge. Data suggest 17% without seizure history had seizures after discharge if PLEDs and 60% if had seizures. Dropouts unclear.

Author, Year Score: 5.0	Kim, 2006, Lancet Neurol; Epilepsy/Unprovoked; Treated Title: Prediction of risk of seizure recurrence after a single seizure and early epilepsy: Further results from the MESS trial. Seizure Types: All types of seizures.
Category	Seizure reoccurrence with immediate treatment of antiepileptic drugs
Study Type	RCT
Conflict of Interest	Sponsored by UK Medical Research Council and Raymond and Beverly Sackler Studentship Award. No mention of COI.
Sample Size	N = 1,443 people who had at least one recent epileptic seizure.
Age/Sex	Mean age: 31.2 years ± 19.1, no other age information provided. 815 males, 628 females.
Comparison	People who had a seizure and immediately started taking drugs to treat it (n = 866) vs. people who had a delayed treatment until their doctor deemed that they were fit to take antiepileptic drugs (n = 577).
Follow-Up	Follow-up after 3, 6, and 12 months.
Results	People with low risk had a prognostic index of ≤ 0.3, medium risk had a prognostic index of 0.3–0.49, and high risk had a prognostic index of ≥ 0.5. No noticeable difference between low-risk people, but medium and high-risk people had great improvements (p = 0.008).
Conclusion	"The model shows that there is little benefit from immediate treatment in patients at low risk of seizure recurrence, but potentially worthwhile benefits are seen in those at medium and high risk"
Comments	Large case series suggesting early antiepileptic drug treatment of minimal benefit.

Author, Year Score: 4*	Kim, 2016, BMC Neurol; Unprovoked/Epilepsy; Treated Title: Clinical predictors of seizure recurrence after the first post-ischemic stroke seizure. Seizure Types: Post-ischemic stroke seizures (specific type not mentioned).
Category	Seizure
Study Type	Observational study
Conflict of Interest	Sponsored by grants from Korea Health Technology R&D Project via Korea Health Industry Development Institute and funding from Ministry of Health and Welfare and Basic Science Research Program via the National Research Foundation of Korea. No COI.
Sample Size	N = 124 patients who had experienced post-stroke seizure after ischemic stroke (PSSi).
Age/Sex	Mean age: 66.3 years, interquartile range of 57.0-75.0, no other age information provided. 69 males, 55 females.
Comparison	Group 1: Patients with early onset PSSi, or onset PSSi within 7 days from stroke onset (n = 48) vs. Group 2: Participants with late onset PSSi, or onset past 7 days of stroke onset (n = 76).
Follow-Up	Follow-up varying with a mean of 44.4 months.

Results	With reference to seizure recurrence, Group 1 experienced 35.4% vs. Group 2 at 48.7%. With reference to factors associated with seizure recurrence, these included atrial fibrillation ($p = 0.016$) and large/cortical stroke lesions ($p < 0.05$) being more common in Group 2 vs. Group 1. Common factors for recurrence for Group 2 were young age, gender (more likely in males), and large lesions vs. Group 1 with factors being gender (again male), atrial fibrillation, and lesions.
Conclusion	"Our study characterized the high-risk group for seizure recurrence in patients with the first PSSi. PSSi patients with high-risk score of seizure recurrence had a greater chance of developing epilepsy later. Therefore, they should be considered for further treatment such as antiepileptic drug medication in clinical practice."
Comments	Retrospective longitudinal case series. Registry based, post-stroke study.

Author, Year Score: 5*	Abraira, 2019, Seizure; Epilepsy; Untreated Title: Long-term epilepsy after early post-stroke status epilepticus. Seizure Types: Not listed.
Category	No treatments were examined
Study Type	Retrospective case series study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 50 patients diagnosed with early-onset post-stroke status epilepticus (PSSE) and no epileptic history.
Age/Sex	Mean age: 74.8 ± 14.3 years, no other age information provided. 28 males, 22 females.
Comparison	Single group was analyzed. No comparison group existed.
Follow-Up	Follow up: Median 214 days (IQR 7.5–747).
Results	10 patients had a seizure at a median of 153 days (IQR 20–334). The estimated rate of epilepsy for Year 1: 35.3% (95% CI: 14.3–46.3%). For Year 2: 53.8% (95% CI: 27.5–80.1%). For univariate analysis, a higher National Institutes of Health Stroke Scale (NIHSS) on stroke onset yielded a higher risk of an epileptic episode occurring ($p = 0.046$). If PSSE > 16h, it was more likely for these patients to have epilepsy at long term. The estimated seizure relapse rate for the first year was 79.5% (95% CI: 41.5–99.1%) vs. 21.8% (95% CI: 7.4–54.8%). For multivariable analysis, NIHSS > 4 ($p = 0.019$; hazard ratio: 7.483; 95% CI: 1.325–42.276) and PPSE episode lasting longer than 16 hours: PSSE > 16h ($p = 0.023$; hazard ratio: 7.483; 95% CI: 1.325–42.276) indicated a higher risk of epilepsy. Mean time to seizure recurrence after PSSE was 142 days (IQR 19–153) for PSSE > 16h and 310 days (IQR 147–480) for PSSE < 16h ($p = 0.094$).
Conclusion	"NIHSS score > 4 at the stroke presentation and PSSE duration > 16h may predict [post-stroke epilepsy] in patients with early-onset PSSE. Recurrence may develop earlier in PSSE patients with longer duration of the episode."
Comments	Retrospective longitudinal case series. Study of post-CVA. Variable follow-up. Median follow-up < 1yr. Worse stroke was associated with increased risk.

Author, Year Score: 4*	Arena, 2017, Mayo Clin Proc; Epilepsy; Untreated Title: Long-term outcome in patients with transient global amnesia: A population-based study. Seizure Types: Not listed.
Category	No treatments were examined
Study Type	Retrospective Nested Case-Control

Conflict of Interest	Sponsored by the Rochester Epidemiology Project. No mention of COI.
Sample Size	N = 442 patients with clinically defined transient global amnesia (TGA).
Age/Sex	Mean age: 64.45 years ± 14.5, no other age information provided. 110 males, 111 females.
Comparison	Patients with TGA (n = 221) vs. age and sex matched controls (n = 221). Diagnosis criteria unspecified.
Follow-Up	Follow-up duration: Mean of 12 years (range, 0.07–29.93).
Results	Diabetes mellitus was more frequent in the control group (p = 0.033). History of migraine was more frequent in the TGA group (p < 0.001). No statistically significant differences between survival curves with endpoints including time to any cerebrovascular event (log-rank P = 0.30), time to seizure event (log-rank P = 0.55), and time to cognitive impair event (log-rank P = 0.88). Median time to death for TGA and control was 22.5 and 17.1 years respectively (log-rank P = 0.34). TGA (Modified Rankin Score (mRS) of 0 with IQR 0–0; range 0–6) and control (mRS of 0 with IQR 0–0; range 0–5) had similar mRS scores at last follow-up.
Conclusion	"Our findings indicate that having an episode of TGA does not increase the risk of subsequent cerebrovascular events, seizures, or cognitive impairment."
Comments	Data suggest TGA is not associated with subsequent seizures.

Author, Year Score: 5*	Choi, 2008, Epilepsia; Epilepsy; Untreated Title: Seizure remission and relapse in adults with intractable epilepsy: A cohort study. Seizure Types: Not listed.
Category	No treatments were examined
Study Type	Retrospective case series study
Conflict of Interest	Sponsored by National Institute of Health. No COI.
Sample Size	N = 187 patients with intractable epilepsy that had: recurrent seizures after 2 or more courses of drug treatment, an average of 1 or more seizure per month for 3 months before index date, aged 18 or more years.
Age/Sex	Mean age: 41 years ± 12.2, minimum aged 18 or more years, no other age information provided. 88 males, 99 females.
Comparison	Group 1, people eligible for study (n =187). Group 2, people who achieved 12 or more months seizure remission (n = 20). Group 3, people who had a seizure after 12 or more months of remission (n = 5).
Follow-Up	Group 1 follow-up: not listed. Group 2 follow-up duration: mean of 3.9 years ± 1.1. Group 3 follow-up duration: mean of 3.5 years ± 1.4.

Results	20 out of 187 patients had ≥ 12 months of seizure remission. Probability of remission year by year: year 1 - 0.6%, year 2 - 4%, year 3 - 8%, year 4 - 13%, year 5 - 18%. No statistical significance was found for the following clinical factors (hazard ratio (HR)): epilepsy syndrome classification (HR data not listed); epilepsy type (HR data not listed); history of surgery (HR: 1.33; 95% CI: 0.31–5.76); status epilepticus (HR: not calculated, lack of convergence); age of onset (HR: 1.07; 95% CI: 0.63–1.82); mental retardation (HR: 0.68; 95% CI: 0.23–2.05); febrile seizure (HR: 1.05; 95% CI: 0.31–3.61); etiology (HR: 1.17; 95% CI: 0.47–2.97); mesial temporal lobe sclerosis (MTS) (HR: 1.31; 95% CI: 0.3–5.65); duration of epilepsy > 10 vs. ≤ 10 years (HR: 0.53; 95% CI: 0.19–1.47); number of failed antiepileptic medications > 5 vs. ≤ 5 with ≥ 12 months of seizure remission (HR: 0.68; 95% CI: 0.28–1.64). 5 of 20 patients had relapse after ≥ 12 months remission. Estimated cumulative probability of relapse was: 0% at year 1, 33% at 2 years, 44% at 3 years. No statistical significance was found for the following clinical factors: History of surgery (HR not calculated, lack of convergence), status epilepticus (HR not calculated, n = 0), age of onset (HR: 0.35; 95% CI: 0.06–1.99), mental retardation (HR: 1.3; 95% CI: 0.13–12.5), febrile seizure (HR: 1.92; 95% CI: 0.31–12), etiology (HR: 0.82; 95% CI: 0.11–5.9), duration of epilepsy > 10 vs. ≤ 10 years (HR not calculated, lack of convergence), number of failed antiepileptic drugs > 5 vs. ≤ 5 with ≥ 12 months remission (HR: 2.9; 95% CI: 0.48–17.7).
Conclusion	"In our prevalence cohort, we found that approximately 4% of adults with long-standing and intractable epilepsy experience 12 months or more of complete seizure remission by second year of follow-up, with additional 4% of subjects per year experiencing this outcome during our study follow-up."
Comments	Longitudinal retrospective case series. Intractable epilepsy. 3-year study. Only 4% achieved remission in 2 years lasting 12 or more months.

Author, Year Score: 3*	Schiller, 2009, Arch Neurol; Epilepsy; Treated Title: Seizure relapse and development of drug resistance following long-term seizure remission. Seizure Types: Not mentioned.
Category	Seizure, antiepileptic drugs
Study Type	Longitudinal case series study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 256 patients who received a newly administered antiepileptic drug treatment.
Age/Sex	Mean age: 31.8 years, no other age information provided. 115 males, 141 females.
Comparison	The comparison was between those who experienced recurrence in their epilepsy after taking their antiepileptic drugs vs. those who did not experience recurrence. Those who did have recurrence were thought to have developed drug-resistant epilepsy.
Follow-Up	Follow-up up to 5 years.
Results	After the end of the follow-up 82% of participants had no recurrency in their seizures whereas 16% did have recurrency in their seizure and developed drug-resistant epilepsy.
Conclusion	"Seizure relapse commonly occurs in patients following long-term seizure remission. Treatment history and duration of epilepsy are predictive risk factors for both seizure relapse and development of drug resistance."
Comments	Data suggest long-term seizure remission does not assure ongoing seizure-free status

Author, Year Score: 5.0	Marson, 2005, Lancet; Epilepsy; Treated/Untreated Title: Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: A randomized controlled trial. Seizure Types: Early epilepsy and single seizures.
Category	Seizure
Study Type	RCT (on behalf of the Medical Research Counsel MESS Study Group)
Conflict of Interest	Sponsored by the UK Medical Research Council. No COI.
Sample Size	N = 1,847 patients with single seizures and early epilepsy, 1,443 of which were randomized.
Age/Sex	Age: median of 24 years, 4.5% between ages of 0-4, 9.3% between ages of 5-9, 33.9% between ages of 10-19. 1,051 males, 796 females.
Comparison	Immediate Treatment: Patients received immediate treatment which consisted of optimum antiepileptic drug chosen by a clinician for the individual patient as soon as possible. Delayed Treatment: Patients received no antiepileptic drugs until the clinician and patient agreed that treatment was necessary.
Follow-Up	Follow-up at 3 and 6 months and 1 year.
Results	Patients in the immediate treatment group had an increased time to first seizure (HR: 1.4, 95% CI: 1.2–1.7), second seizure (HR: 1.3, 95% CI: 1.1–1.6), and first tonic-clonic seizure (HR: 1.5, 95% CI: 1.2–1.8). Results also indicate that immediate treatment reduced the time it took to achieve 2-year remission of seizures ($p = 0.023$). At follow-up, 76% of patients in the immediate treatment group and 77% of patients in the delayed treatment group were free of seizures between 3–5 years (95% CI: 5.8–5.5%).
Conclusion	"Immediate antiepileptic drug treatment reduces the occurrence of seizures in the next 1–2 years but does not affect long-term remission in individuals with single or infrequent seizures."
Comments	Data suggest minimal benefit from early antiepileptic drugs treatment. Included those with 1 or more seizures consistent with early epilepsy.

Author, Year Score: 3*	Friedman, 2012, Epilepsy Behav; Epilepsy; Untreated Title: Do recurrent seizure-related head injuries affect seizures in people with epilepsy? Seizure Types: Epilepsy.
Category	Seizure
Study Type	Longitudinal analysis
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 204 patients with history of seizures and documented head injuries.
Age/Sex	Mean age: 34.9 years, no other age information provided. 97 males, 107 females.
Comparison	Group 1: patients experienced a seizure-related head injury (SRHI) (n = 37) vs. Group 2: patients experienced a non-SRHI (n = 167).
Follow-Up	Follow-up at 6, 12, 18 and 24 months.
Results	There was no significant difference found in the two groups for the progression rate of seizure frequencies for the 2 years that patients were followed ($p = 0.518$). A statistically significant outcome found was that the variability in progression rates was higher for Group 1 than Group 2 ($p < 0.01$).

Conclusion	"Though seizure frequency varied following head injury, overall seizure frequency was not significantly impacted by presence or absence of SRHI over the 2-year study period. Changes in seizure semiology were not observed in those with SRHIs. Although mild SRHI is common among PWE, it does not appear to influence seizure characteristics over a relatively short period."
Comments	Retrospective longitudinal case series. TBI study among those with epilepsy. Mild injury did not increase risks.

Author, Year Score: 5*	Lhatoo, 2001, J Neurol Neurosurg Psychiatry; Epilepsy; Treated Title: The dynamics of drug treatment in epilepsy: An observational study in an unselected population-based cohort with newly diagnosed epilepsy followed up prospectively over 11–14 years. Seizure Types: Epilepsy.
Category	Seizure, Antiepileptic medication
Study Type	Longitudinal case series study
Conflict of Interest	Sponsored by grants from Brain Research Trust, the National Society for Epilepsy, the National Hospital for Neurology and Neurosurgery, and Action Research for grants to support the National General Practice Study of Epilepsy (NGPSE). No mention of COI.
Sample Size	N = 564 patients with definite epilepsy.
Age/Sex	Data on mean age and sex not provided.
Comparison	Of the total patients, 433 were prescribed medication upon first visit. Of those started on therapy, the breakdown is as follows: phenytoin (n = 161), carbamazepine (n = 154), valproate (n = 84), phenobarbital (n = 14), and others (n = 20).
Follow-Up	Follow-up annually for 11–14 years
Results	Approximately 16% of patients changed medication due to a lack of efficacy. And 20% of all patients did not reach 5-year terminal remission, thus the authors calculated the incidence rate of not reaching terminal remission to be 6,000/30,000.
Conclusion	"Out of 30,000 patients with newly diagnosed epilepsy every year in the United Kingdom, about 6,000 have inadequate seizure control in the long term. About a third of the patients in this group have one or more seizures every month. Only two thirds of these patients with frequent seizures are likely to switch medication to try and achieve better seizure control. There is probably still considerable room for improvement in prescribing practice in the United Kingdom."
Comments	Longitudinal case series. Reduced antiepileptic drugs use with time. Dropouts low.

Author, Year Score: 3.5	Cardoso, 2003, Arq Neuropsiquiatr; Epilepsy; Treated/Untreated Title: Is low antiepileptic drug dose effective in long-term seizure-free patients? Seizure Type: Epilepsy
Category	Seizure, epilepsy
Study Type	Prospective randomized study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 94 patients who had been seizure-free for at least 2 years.

Age/Sex	Median age: 30.3 years, minimum age of 14. 50 males, 44 females.
Comparison	Full antiepileptic drug withdrawal (n = 45) vs. partial antiepileptic drug withdrawal which ended with a 50% reduction of total dosage (n = 49).
Follow-Up	Follow-up period of 2 years.
Results	Seizure recurrence in group one was 34.04% compared to 32.69% in group 2. Survival analysis showed that there was no difference in recurrence between the two groups (p = 0.8 group 1:0.89, 0.80, 0.71 and 0.69; group 2: 0.86, 0.82, 0.75 and 0.71).
Conclusion	"Leaving seizure-free patients on low antiepileptic drugs dose did not reduce the risk for seizure recurrence. That is, once the decision of antiepileptic drugs withdrawal has been established, it should be complete."
Comments	Modest sample size. Data suggest no statistical benefit from low dose antiepileptic drugs.

Author, Year Score: 3*	Beghi 1988, Epilepsia; Epilepsy; Treated Title: Prognosis of epilepsy in newly referred patients: A multicenter prospective study. Seizure Types: Tonic-clonic.
Category	Seizure, epilepsy
Study Type	Prospective study
Conflict of Interest	Sponsored by National Research Council Grant on Preventive and Rehabilitative Medicine. No mention of COI.
Sample Size	N = 283 patients with afebrile seizures.
Age/Sex	Range of ages: 19 under 4, 60 between 5–9, 103 between 10–19, and 101 aged 20 or older. 160 males, 123 females.
Comparison	All patients were started on monotherapy and a standard daily dosage of antiepileptic drugs. Comparison done between those who relapsed and those who did not.
Follow-Up	Follow-up average of 21.6 months.
Results	A total of 146 patients experienced relapse. The risk of recurrence was 36% at 3 months, 43% at 6 months, 49% at 1 year.
Conclusion	"Patients with severe epilepsy are a small subset of our sample, essentially characterized by late onset of epilepsy, higher number of seizures, long disease duration before treatment, partial seizures, presence of etiologic factors and/or epileptiform EEG abnormalities."
Comments	Data provided on seizures after antiepileptic drug treatment.

Author, Year Score: N/A	Kalita, 2005, Electromyogr Clin Neurophysiol; Epilepsy; Treated Title: Predictors of one-year seizure remission: A clinicoradiological and electroencephalographic study. Seizure Types: Epilepsy.
Category	Seizure, epilepsy
Study Type	Longitudinal case series study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 120 patients who had consecutive epilepsy.

Age/Sex	Mean age: 26.8 years, range 13-71. 86 males, 34 females.
Comparison	Patients classified in idiopathic (n = 48) vs. symptomatic (n = 53) vs. cryptogenic (n = 19). These three groups were then compared based on relapse after using antiepileptic drugs.
Follow-Up	Follow-up after 1 year.
Results	Of all the patients, 90 were seizure-free after 1 year in the study, 78 were on monotherapy, 12 on duo therapy, and none on at least 2 types of antiepileptic drugs. Remission rate was dependent on the type of epilepsy ($X2 = 91.8$, $df = 4$, $p < 0.001$).
Conclusion	"75% epileptic patients had 1-year seizure remission; majority achieved on monotherapy, occasionally on duo therapy and none on more than 2 antiepileptic drugs. Symptomatic epilepsy due to ring lesion had higher seizure remission rate followed by idiopathic. Cryptogenic epilepsy, frequent seizure, neurological deficit and EEG abnormalities were related to poor remission and requirement of a greater number of antiepileptic drugs."
Comments	Data on seizure recurrences in a modest sized case series.

Author, Year Score: 2.5	The Medical Research Council Antiepileptic Drug Withdrawal Study (MRCADWS), 1991, Lancet; Epilepsy; Treated/Untreated Title: Randomized study of antiepileptic drug withdrawal in patients in remission. Medical Research Council Antiepileptic Drug Withdrawal Study Group. Seizure Types: Epilepsy.
Category	Seizure, epilepsy
Study Type	RCT
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 1013 patients who were seizure-free for at least 2 years.
Age/Sex	Mean age: 26.5 years, no other information on age was provided. 496 males, 517 females.
Comparison	Those who had no withdrawal of antiepileptic drugs (n = 503) vs. patients who were slowly taken off their antiepileptic drugs (n = 510).
Follow-Up	Follow-up after 3 months, 6 months, 1 year, and yearly thereafter.
Results	After a total of 2 years 78% of those who had remained on their antiepileptic drugs had not experienced a recurrence in seizure. Whereas 59% of those who were slowly taken off antiepileptic drugs experienced a seizure within those 2 years. After the 2-year follow-up differences in the groups diminished.
Conclusion	"The most important feature of this study is the determination of relative risks of seizure recurrence for patients who elect to withdraw antiepileptic drugs rather than to continue them after a period of remission. The stratified proportional hazards model used allows the development of a statistical model for prediction of relapse with the two policies in this trial. Validation in this patient population may help in counselling patients who will ultimately have to decide whether they wish to continue with antiepileptic drug treatment."
Comments	RCT, with comparisons of those on/off antiepileptic drugs

Author, Year Score: 2*	Specchio, 2001, J Neurol Neurosurg Psychiatry; Epilepsy; Treated/Untreated Title: Discontinuing antiepileptic drugs in patients who are seizure-free on monotherapy. Seizure Types: Epilepsy.
Category	Seizure, epilepsy
Study Type	Longitudinal case series study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 330 patients who were seizure-free for the last 2 years.
Age/Sex	Range of age: 42 under 15, 235 between 15–34, 40 between 35–54, and 13 over 54, no other information on age was provided. 145 males, 185 females.
Comparison	Patients who were taken off their antiepileptic drug treatment (n = 225) vs. patients who continued their treatment of antiepileptic drugs (n = 105).
Follow-Up	Follow-up after 45 to 50 months.
Results	Of the patients continuing their treatment with antiepileptic drugs 29 of them experienced a relapse. Of the patients who were taken off their antiepileptic drugs 113 of them had a relapse. Active disease, number of years of remission, and abnormal psychiatric findings seemed to have a relation.
Conclusion	"Seizure-free referral patients on stable monotherapy who elect to withdraw drug treatment are at higher risk of seizure relapse compared with patients continuing treatment. Severity of disease and seizure-free period are significant prognostic factors."
Comments	Moderate sized case series, providing data on/off antiepileptic drugs over approximately 4 years.

Author, Year Score: 3.0	Callaghan, 1988, N Engl J Med; Epilepsy; Treated Title: Withdrawal of anticonvulsant drugs in patients free of seizures for two years. Seizure Types: Epilepsy.
Category	Seizure, epilepsy
Study Type	RCT
Conflict of Interest	Sponsored by Parke-Davis Research Laboratories. No mention of COI.
Sample Size	N = 92 patients who had been seizure-free for at least 2 years.
Age/Sex	Mean age: 24 years, no other information on age was provided. 40 males, 52 females.
Comparison	The comparison was between those who had relapsed after being taken off their anticonvulsant drugs.
Follow-Up	Follow-up after a mean of 35 months.
Results	Of all the patients 31 had relapsed. Of the entire population 35 of them were underage of 15 and 11 experienced relapse. The underage population did not experience a significant difference in relapse rate from the adult population ($p = 0.359$, chi-square test).
Conclusion	"We conclude that withdrawal of anticonvulsant medication should be considered in patients free of seizures for two years."
Comments	Data on antiepileptic drug discontinuation.

Author, Year Score: 4.0	Heller, 1995, J Neurol Neurosurg Psychiatry; Epilepsy; Treated Title: Phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed adult epilepsy: A randomized comparative monotherapy trial. Seizure Types: Tonic-clonic.
Category	Seizure, epilepsy
Study Type	RCT
Conflict of Interest	No mention of COI or sponsorship.
Sample Size	N = 243 patients who had experienced tonic-clonic seizures.
Age/Sex	Median age: 29 years, all were 16 years or older. 117 males, 126 females.
Comparison	Phenobarbitone dosage 60 mg/day (n = 58) vs. phenytoin dosage 200 mg/day (n = 63) vs. carbamazepine dosage 400 mg/day (n = 61) vs. sodium valproate dosage 400 mg/day (n = 61).
Follow-Up	Follow-up median was at 30 months.
Results	After a 3-year follow-up 27% were seizure-free (95% CI 20–23). Of all the patients 75% had achieved a one-year remission (95% CI 69–82). There was no significant difference between the four different types of drugs.
Conclusion	"[W]e have found no significant differences in the efficacy of phenobarbitone, phenytoin, carbamazepine, or sodium valproate in newly diagnosed previously untreated adult patients with two or more tonic-clonic or partial seizures with or without secondary generalization."
Comments	Data suggest equivalency across various antiepileptic drugs, with seizure recurrence data provided.

Author, Year Score: 3*	Elwes, 1984, N Engl J Med; Epilepsy; Treated Title: The prognosis for seizure control in newly diagnosed epilepsy. Seizure Types: Epilepsy, tonic-clonic.
Category	Seizure, epilepsy
Study Type	Prospective study
Conflict of Interest	Sponsored by Medical Research Council, Ciba-Geigy, Parke-Davis, Labaz, and the British United Provident Association. No mention of COI.
Sample Size	N = 106 patients with previously untreated tonic-clonic, partial, or mixed seizures.
Age/Sex	Median age: 23 years, range 6–77, no other information on age was provided. 51 males, 55 females.
Comparison	Patients were treated with phenytoin (n = 61) vs. bamazepine (n = 45). Both were then compared based on the amount of relapse in the group.
Follow-Up	Follow-up of 6 years.
Results	Of all the patients, 80 experienced relapses: 35 after two months, 44 after 4 months, 51 by six months, and 62 by one year. Presence of partial seizures ($X2 = 9.1$, d.f. = 2, $p = 0.011$), family history of epilepsy ($X2 = 5.4$, d.f. = 1, $p = 0.02$), high frequency of tonic-clonic seizures beforehand ($X2 = 5.3$, d.f. = 1, $p = 0.022$), or neurologic handicap ($X2 = 3.8$, d.f. = 1, $P = 0.022$), social handicap ($X2 = 11.6$, d.f. = 1, $p < 0.001$), or psychiatric handicap ($X2 = 4.3$, d.f. = 1, $p < 0.038$) were associated with worse prognosis.
Conclusion	"[T]he long-term pattern of seizure control is largely established during the first two years of treatment."
Comments	Data regarding seizure recurrences over 6 years.

Author, Year Score: 2*	Nakazawa, 1995, Psychiatry Clin Neurosci; Epilepsy; Untreated Title: Prognosis of epilepsy withdrawn from antiepileptic drugs. Seizure Types: Epilepsy.
Category	Epilepsy, antiepileptic drugs
Study Type	Prospective study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 55 patients who had been seizure-free for at least 2 years.
Age/Sex	Mean age: 18.2, 13 between the ages of 0 to 9, 20 between the ages of 10 and 19. 27 males, 16 females.
Comparison	Patients were taken off antiepileptic drugs and compared by who had relapsed and who had not relapse.
Follow-Up	Follow-up ranged from 0.9 to 8.8 years.
Results	Of the 43 patients none of them relapsed once their antiepileptic medications were halted.
Conclusion	"Finally, we want to discuss two points briefly. One is concerned with the interval from the onset of reduction in antiepileptic drugs to their discontinuation. At present, we tentatively propose that about a 2-year period would be appropriate because it is shown that a rapid reduction in antiepileptic drugs and benzodiazepine is known to induce withdrawal seizures."
Comments	Data provided for seizure recurrence after antiepileptic drug withdrawal.

Author, Year Score: 6*	Kotsopoulos, 2005, Lancet; Epilepsy; Unprovoked Title: Incidence of epilepsy and predictive factors of epileptic and non-epileptic seizures. Seizure Types: Not mentioned.
Category	Seizure, epilepsy
Study Type	Prospective population-based study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 268 patients with a first seizure or who had undiagnosed seizures.
Age/Sex	Age: mean of 49 for men and 51 for women, range: 40 between 14–24 years old, 45 between 25–44 years old, 86 between 45–64 years old, and 97 over 65 years old, no other information on age was provided in the study. 137 males, 131 females.
Comparison	Patients who were experiencing epilepsy (n = 94) vs. patients who were experiencing a first unprovoked seizure (n =174).
Follow-Up	Follow-up after 6 months.
Results	For those patients with unprovoked seizures, 45.7% had a n index seizure, 17.9% had more than 5 recurrent seizures. The kappa value for the inter-rater agreement gave good results (0.92, 95% CI: 0.88–0.96).

Conclusion	"Non-epileptic seizures are often misdiagnosed as epileptic seizures. Obviously, in case of a single seizure, the potential of misdiagnosis is increased. The predictive factors found in this study may assist clinicians in the diagnosis of seizures. Hence, based on certain issues such as findings from diagnostic tests (CT or EEG), they may distinguish patients with epileptic seizures from patients with non-epileptic seizures."
Comments	Data suggest risk factors for seizures include EEG, hypertension, cardiovascular disease, head injury, and female sex.

Author, Year Score: 5.5	Bonnett, 2010; Unprovoked, BMJ; Treated/Untreated; Secondary Analysis of MESS Trial Title: Risk of recurrence after a first seizure and implications for driving: Further analysis of the multicenter study of early epilepsy and single seizures. Seizure Types: Early epilepsy and single seizures.
Category	Seizure
Study Type	RCT
Conflict of Interest	Sponsored by grants from the National Institute for Health Research. No mention of COI.
Sample Size	N = 1,443 patients with single unprovoked seizures.
Age/Sex	No mention of mean age or sex.
Comparison	Immediate Treatment: Patients received immediate treatment for single unprovoked seizures vs. Delayed Treatment: Patients received delayed treatment for single unprovoked seizures.
Follow-Up	Follow-up at 6, 12, 18, and 24 months.
Results	Patients in the immediate treatment group had a 14% risk of seizure recurrence after a seizure-free period of six months (95% CI (CI: 10–18%) compared to 18% risk of seizure recurrence in the delayed treatment group (95% CI: 13–23%). After 12 months, the delayed treatment group had a risk of 10% (95% CI: 6–15%).
Conclusion	"After a seizure-free period of six months following a first seizure the overall risk of a recurrence was low enough (below 20%) to allow people to resume driving, irrespective of whether they had started antiepileptic."
Comments	Third report of MESS trial

Author, Year Score: 5	Bonnett, 2017, BMJ; MESS trial, secondary analysis; Unprovoked; Treated Title: Risk of a seizure recurrence after a breakthrough seizure and the implication for driving: Further analysis of the standard versus new antiepileptic drugs (SANAD) randomized controlled trial. Seizure Types: Epileptic seizures; mention of myoclonic, absence, and tonic-clonic seizures.
Category	Antiepileptic drugs: carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate, valproate
Study Type	Secondary analysis of randomized controlled trial (RCT)
Conflict of Interest	Sponsored by National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care, Northwest Coast. No COI.
Sample Size	N = 399 patients greater than 16 years of age who had a history of at least 2 clinically significant epileptic seizures within the last year, had no seizure for 12 months when receiving treatment, and had maintained or increased medication dosage 6 months before having a breakthrough seizure.

Age/Sex	Mean age: Not provided. Median age: 38.3 years (IQR 24.3–53.5 years), all above 16 years old. 231 males, 168 females.
Comparison	Single group comprised of participants from both Arm A and Arm B of the SANAD RCT. (N = 286) patients came from Arm A, which consisted of 1721 patients assigned to carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate in a 1:1:1:1:1 ratio vs. (n = 113) came from Arm B, which consisted of 716 patients assigned to valproate (considered as the standard of care), lamotrigine, or topiramate in a 1:1:1 ratio.
Follow-Up	1 month, 2 months, 6 months, 1 year, 2 years.
Results	Probability of a seizure by 12 months was 70.1%. The number of people and the percentage of the population that had a seizure by the specified period is: 1 month - 111 people (28%), 2 months - 166 people (42%), 6 months - 214 people (54%), 1 year - 242 people (61%), 2 years – 254 people (64%). At 6 months the risk of having another seizure is significantly greater than 20%. At 12 months the risk of having another seizure is significantly less than 20% based on a 95% confidence interval (CI).
Conclusion	"Twelve months appears to be an appropriate time off driving for patients of driving age who have experienced a period of at least 12 months initial seizure freedom followed by a breakthrough seizure. Provided that patients remain seizure-free for 12 months following a breakthrough seizure, their risk of a seizure in the next 12 months would be less than the 20% risk standard that informs the UK legislation and [Driver and Vehicle Licensing Agency] guidance."
Comments	RCT of comparing antiepileptic drugs for those with 2 or more unprovoked seizures in past year. Combined analyses. Two arms differed by family history (8% vs. 19%), seizure type, EEG, CT, and age at first breakthrough seizure.

Author, Year Score: 2.5	Chadwick, 1996, Epilepsia; Provoked/Unprovoked; Treated Title: Outcomes after seizure recurrence in people with well-controlled epilepsy and the factors that influence it. Seizure Types: All types.
Category	Medications, seizures
Study Type	Longitudinal case series study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 409 patients with recurrent seizures.
Age/Sex	No mention of age or sex.
Comparison	Patients were placed on antiepileptic drugs and were monitored for 6 months to see how often recurrences occurred. If patients were to die the study would cease from following that patient, but still include them.
Follow-Up	Follow-up after 6 months, 1 year, and 2 years.
Results	Of all the patients, 51% of them were able to remain seizure-free (95% confidence limits 45, 56%) within the first year and 40% within 2 years (95% confidence limits 35, 45).
Conclusion	"Our results provide no evidence that discontinuation of antiepileptic drugs modifies the long-term prognosis of a person's epilepsy, although it does increase the risk of seizures in the 1- to 2-year period after discontinuation."
Comments	Data suggest reduced risk of recurrence among those on antiepileptic drugs.

Author, Year Score: 3*	Kumar, 2019, Acta Neurol Scand; Unprovoked; Treated Title: Seizure recurrence risk in persons with epilepsy undergoing antiepileptic drug tapering. Seizure Types: Focal onset and generalized onset seizures (myoclonic excluded).
Category	Seizure
Study Type	Observational study
Conflict of Interest	Sponsored by (partial) funding from Project A-428 Institute Research Grant via All India Institute of Medical Sciences in New Delhi. No COI.
Sample Size	N = 438 persons with epilepsy (PWE) undergoing antiepileptic drug tapering.
Age/Sex	Mean age: 25.4 years, no other data about age. 245 males, 163 females.
Comparison	Group 1: PWEs who were receiving monotherapy including antiepileptic drugs such as valproate (VPA, up to 60 mg/kg tapering off), carbamazepine (CBZ, up to 35 mg/kg tapering off), phenytoin (PHT, up to 6 mg/kg tapering off), levetiracetam (LEV, up to 60 mg/kg tapering off), or clobazam (CLB, max dose not included) (n = 181) vs. Group 2: PWEs who were receiving polytherapy involving the same antiepileptic drugs listed above (n = 227).
Follow-Up	Follow-up ranging from 19–41 months.
Results	Examining the level of seizure recurrence risk in PWEs found no difference between types of therapy. Group 1 had 25.9% vs. Group 2 at 31.7% ($p = 0.09$). Both groups' risk for seizure recurrence was highly related to characteristics such as history of smoking ($p = 0.003$), history of failing antiepileptic drug tapering ($p = 0.04$), frequency of seizures ($p = 0.002$), and duration of epilepsy ($p = 0.03$).
Conclusion	"There is a wide variation in antiepileptic drug tapering pattern and seizure recurrence risk can be minimized by considering the risk factors like history of smoking/alcohol/tobacco, longer duration of epilepsy, frequency of seizures before control, and previously failed tapering."
Comments	Prospective longitudinal case series regarding tapering. Up to 3.5 years of follow-up study.

*Study design may be reclassified, especially from "cohort" to "longitudinal case series study" for those studies consisting of a series of patients followed longitudinally.

APPENDIX E: EPILEPSY SURGERY AND SUBSEQUENT RISK OF SEIZURES

Author, Year Score: N/A	Jeha, 2007, Brain; Surgery Title: Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. Seizure Types: Pharmacoresistant epilepsy or refractory epilepsy.
Category	Seizure, surgery
Study Type	Retrospective longitudinal case series
Conflict of Interest	No mention of COI or sponsorship.
Sample Size	N = 70 patients who had a frontal lobectomy surgery between 1995 and 2003.
Age/Sex	Mean age: 22 years, range 1-57, no other statements made about age. 40 males, 30 females.
Comparison	Seizure-free: Patients who stopped having seizure after they had undergone frontal lobectomy surgery vs. Recurring Seizures: Patients who kept having seizures after their frontal lobectomy surgery
Follow-Up	Follow-up after 4 years.
Results	Out of the 70 patients, 55.7% of them were initially seizure-free after the surgery (95% CI = 50–62, $p < 0.0001$). After 5 years only 30.1% of patients were still seizure-free (95% CI = 21–39, $p < 0.0001$). The rate of post-surgical seizures was 2.17 (95% CI = 1.50–3.14, $p < 0.0001$).
Conclusion	"We report the first longitudinal outcome study on 70 [frontal lobe epilepsy] patients evaluated using modern diagnostic techniques. We show that frontal lobectomy can be a successful treatment option in selected patients with refractory epilepsy, with long-term seizure-freedom rates of up to 40%. Eighty per cent of seizure recurrences occur within the first 6 months following surgery. Ideal surgical candidates are those in whom there is MRI and electrophysiological evidence of epileptogenicity that is restricted to the frontal lobe, and in whom a complete resection of the epileptogenic zone is possible."
Comments	Longitudinal case series (n = 70) with data suggesting cumulative seizure rate of approximately 70% by 5 years, while approximately 30% seizure-free at 5 years. Only 22 patients available for estimated risk at 5 years. Antiepileptic drug uses unclear.

Author, Year Score: 2*	Bauer, 2007, Acta Neurochir (Wien); Surgery Title: Outcome of adult patients with temporal lobe tumors and medically refractory focal epilepsy. Seizure Types: Medically refractory focal epilepsy.
Category	Seizure, epilepsy
Study Type	Retrospective study
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 14 patients with temporal lobe epilepsy.
Age/Sex	Mean age: 32.2 years, range 17-52, no other age statement made. 4 males, 10 females.
Comparison	Patients who had temporal lobe resection (n = 3) vs. patients who had extended lesionectomy (n = 4) vs. extended lesionectomy with resection of emporomesial structures (n = 7). These surgery types were compared to see if temporal lobe epilepsy was caused.

Follow-Up	Follow-up after 3, 6, and 12 months.
Results	The Engel classification placed 9 patients in the IA class, 3 in the IC, and 1 in both IIIA and IVA. The classification from the ILAE classification put 12 patients in class 1 and 2 patients in class 4. Of the patients 3 of them showed homonymous quadrantanopia.
Conclusion	"Patients with drug resistant epilepsy as the main presentation of temporal lobe tumors should undergo evaluation in dedicated epilepsy surgery programs. The procedure should include diagnosis of the type of tumor by advanced imaging and radio-nuclear methods followed by rapid determination of intractability to antiepileptic drug treatment. In instances of drug refractoriness, a presurgical work-up should be performed without unnecessary delay. According to our results, tailored surgery should be performed, which offers seizure freedom in 86% of patients."
Comments	Small case series of 11 patients with medically refractory epilepsy. Did not report rates of seizures.

Author, Year Score: 4*	De Tisi, 2011, Lancet; Surgery Title: The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: A cohort study. Seizure Types: Refractory focal epilepsy.
Category	Seizure, surgery
Study Type	Prospective study
Conflict of Interest	No COI. Sponsored by UK Department of Health, National Institute for Health Research and Biomedical Research Centres.
Sample Size	N = 615 adults (497 anterior temporal resections, 40 temporal lesionectomies, 40 extratemporal lesionectomies, 20 extratemporal resections, 11 hemispherectomies, and 7 palliative procedures [corpus callosotomy, subpial transection])
Age/Sex	No mention of mean age, range 16–63 years, no other statement about age of participants was made. 287 male, 328 female.
Comparison	Seizure-free: Patients who after undergoing surgery had no recurring seizures afterwards. Some did have simple partial seizures, but no major seizures. vs. Non-seizure-free: Patients who kept having recurring seizures before the follow-up.
Follow-Up	Follow-up after 1 and 5 years.
Results	Extratemporal resections had seizure recurrences more often than anterior lobe resection ($p = 0.02$). The results show that 52% of the participants were seizure-free after the follow-up (95% CI 48–56, $p = 0.02$).
Conclusion	"For seizure outcome, surgery is successful for many individuals in whom antiepileptic drugs have not been effective, but further improvements need to be made to presurgical assessment to further increase rates of success."
Comments	None

Author, Year Score: 6*	McIntosh, 2004, Brain; Surgery Title: Temporal lobectomy: Long-term seizure outcome, late recurrence, and risks for seizure. Seizure Types: Mention of tonic-clonic seizures.
Category	Anterior temporal lobectomy
Study Type	Retrospective study
Conflict of Interest	Sponsored by the Australian National Health and Medical Research Council, the Austin Hospital Medical Research Foundation, and the Epilepsy Association, Australia. No mention of COI.

Sample Size	N = 325 patients who had an anterior temporal lobectomy performed between 1987 and 1998.
Age/Sex	Age at surgery: range = 1.6–51.4 (IQR 12.0–25.4). Age at onset: range = 0.25–40 (IQR 3–16). Sex: not listed.
Comparison	Groups according to pre-op pathology: foreign tissue lesion (FTL) (n = 51) vs. hippocampal sclerosis (HS) (n = 201) vs. normal temporal lobe (n = 33) vs. other (n = 16) vs. distant lesion (n = 24).
Follow-Up	Follow-up mean: 9.6 ± 4.2 years.
Results	190 of 325 patients had post-op seizures. Probability of post-op seizure at 3 months was 78.5% with this percentage decreasing by 2.7 to 5.6% over the next five years. Probability of post-surgery, full seizure remission at: year 1 – 60.9% (95% CI: 55–56), year 2 – 55.3% (95% CI: 50–61), year 5 – 47.7% (95% CI: 4 –53), year 10 – 41% (95% CI: 36–48), and year 15 – 36.8% (95% CI: 30–44). Based on all available patient evidence (best evidence), FTL and HS groups had a higher probability (51% (95% CI: 30.2–68.6) and 42.6% (95% CI: 33.5–51.3) respectively) of complete recovery at 15 years post-op. The remaining groups at 15 years had 0 cases remaining for analysis or probability or CI was not calculated for that group. Use of antiepileptic drugs did not increase recurrence (HR: 1.03, 95% CI: 0.5–2.1).
Conclusion	"The results of this study indicate that the lack of an obvious abnormality or the presence of diffuse pathology, and preoperative secondarily generalized seizures are risk factors for recurrence after surgery. Late recurrence after initial seizure freedom is not a rare event; risk factors specific to this phenomenon are unidentified."
Comments	Retrospective case series over 20 years. Unclear dropout rate over time. Recurrence risk differs by type.

Author, Year Score: 4*	Lüders, 1994, Epilepsia; Surgery Title: Quantitative analysis of seizure frequency 1 week and 6, 12, and 24 months after surgery of epilepsy. Seizure Types: Not specified.
Category	Seizure, surgery
Study Type	Quantitative analysis
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 71 operated on patients.
Age/Sex	No mention of age. 44 males, 27 females.
Comparison	Patients who did and did not have seizures after their surgery.
Follow-Up	Follow-up after 2 years.
Results	Post operation the outcome of seizures was stable for the 6-month follow-up except for recurrence in initially seizure-free patients. People who had a seizure decrease at 6 months continued to have seizures at 1 and 2 years, but as time went on people increasingly joined the seizure decrease group. Chi-square test was used to see how frequency of seizures compared at 6 months and 2 years (chi square = 56.6; $p < 0.01$).
Conclusion	"Finally, the lack of difference regarding outcome between patients with temporal and extratemporal epilepsy in this study may well be related to the rather small sample of extratemporal cases. Additional studies with many extratemporal cases will be necessary to determine this issue."
Comments	Longitudinal case series of 99 patients with partial seizures found 56 (79%) were seizures free at 6 months, 53 (75%) at 1 year, and 47 (66%) were seizure-free at 2 years.

Author, Year Score: 2*	Schramm, 2001, J Neurosurg; Surgery Title: Surgical treatment for neocortical temporal lobe epilepsy: Clinical and surgical aspects and seizure outcome. Seizure Types: Neocortical temporal lobe epilepsy.
Category	Seizure, surgery
Study Type	Prospective study
Conflict of Interest	Sponsored by Deutsche Forschungemeinschaft, Sonderforschungbereich 400, and Subproject B1. No mention of COI.
Sample Size	N = 62 patients who have neocortical temporal lobe epilepsy.
Age/Sex	Mean age: 27.9 years, range 6-60 years, no specific age statements. 27 males, 34 females.
Comparison	Follows patients with epilepsy after their surgery to help stop their temporal lobe epilepsy (TLE) and observe the patient's recurrence vs. those who had no recurrence.
Follow-Up	Follow-up after 21.9 ± 14 months
Results	Class I on the seizure outcome scale meaning they were seizure-free, 90% of these people experienced improvement in their frequency of seizures. Class II no more than 2 seizures a year, this group had a 79% improvement. Class III 75% reduction in frequency. Class IV less than 75% improvement in frequency. When Class I and II are combined and Class III and IV are combined there is no statistical significance ($\alpha = 0.05$).
Conclusion	"These results demonstrate that the concept of lateral or neocortical TLE as a distinct entity is useful. Surgery for neocortical TLE can be considered a viable treatment option that is associated with a low morbidity rate and good outcomes"
Comments	Longitudinal case series of 61 heterogenous causes of neocortical TLE found improvements after surgery for neocortical TLE, although absolute rates over time were not reported. Data suggest surgery reduces seizure risk but does not eliminate it.

Author, Year Score: N/A	Uribe-San-Martin, 2018, Epilepsy Res; Surgery Title: Corpus callosum atrophy and post-surgical seizures in temporal lobe epilepsy associated with hippocampal sclerosis. Seizure Types: Not specified.
Category	Seizure, surgery
Study Type	Retrospective study
Conflict of Interest	No COI. Sponsored by European Committee for Treatment and Research in Multiple Sclerosis.
Sample Size	N = 74 patients with multiple sclerosis and epilepsy who underwent temporal lobe surgeries.
Age/Sex	Mean age: 36.4 years, range 25−55. 32 males, 42 females.
Comparison	Multiple sclerosis patients with epilepsy who underwent epilepsy surgery (n = 40) vs. higher corpus callosum index rate than patients with multiple sclerosis without epilepsy who underwent epilepsy surgery (n = 15).
Follow-Up	Follow-up average 6.4 years.
Results	PWE seemed to have a higher rating on the corpus callosum index (CCI) than patients with no epilepsy ($p = 0.007$). Male gender and corpus callosum index atrophy rates seemed to be a good predictor in whether a patient would have seizure recurrences (HR:1.21, $p = 0.001$).

Conclusion	"We demonstrated that atrophy of the corpus callosum, using the CCI, is related with poor seizure control in two different neurological disorders presenting with epilepsy, which might suggest that corpus callosum atrophy obtained in early post-surgical follow-up, could be a biomarker for predicting recurrences and guiding treatment plans."
Comments	Population of multiple sclerosis patients with temporal lobe seizures, rather than a general population.

Author, Year Score: N/A	Boran, 2019, Clin Neurophysiol; Surgery Title: High-density ECoG improves the detection of high frequency oscillations that predict seizure outcome. Seizure Types: Drug-resistant focal epilepsy.
Category	Seizure, diagnostic
Study Type	Retrospective cross-sectional
Conflict of Interest	Sponsored by grants from the Swiss National Science Foundation. No COI.
Sample Size	N = 22 patients who underwent resective epilepsy surgery.
Age/Sex	Mean age: 19.91 years, 13 of 22 patients were less than 18 years old, range 3−17. 10 males, 12 females.
Comparison	Group 1: Patients' fast ripples (FR) rates analyzed in surgery with standard 10 mm inter-contact spacing electrodes (ECoG) (n = 14) vs. Group 2: Patients FR was analyzed with 5 mm spacing high-density grid (hd-ECoG) electrodes (n = 8).
Follow-Up	Follow-up between 18 to 35 months.
Results	The primary outcome of this study was to test the ECoG vs. the hd-ECoG for FR detection. Although the FR amplitude and rates were higher with the hd-ECoG group, the results were not statistically significant (p = 0.4559). Maximum FR event rate was determined to be higher for the hd-ECoG group (p = 0.0360).
Conclusion	"We found that hd-ECoG, when compared to standard-ECoG, 1) increased the number of detected FR and 2) improved the prediction of seizure outcome based on FR. The main advantage of hd-ECoG over standard ECoG is that it enables denser spatial sampling of FR generators. Hd-ECoG may thereby advance seizure freedom after epilepsy surgery."
Comments	Study does not address risk of seizures, rather is a diagnostic study.

*Study design may be reclassified, especially from "cohort" to "longitudinal case series study" for those studies consisting of a series of patients followed longitudinally.

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APPENDIX F: REQUIREMENTS OF STATES AND SELECT COUNTRIES REGARDING DRIVERS WITH SEIZURES

Table 4. State commercial driving requirements.

State	State commercial driving requirements
Alabama	Adopted FMCSA's medical standards to obtain a commercial driver's license. No waivers are granted. May not be licensed to drive taxis or school buses.
Alaska	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers.
Arizona	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers.
Arkansas	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers. Not qualified to drive school buses.
California	Adopted FMCSA's medical standards to obtain a commercial driver's license. On original applications, rare exceptions may be made to the medical requirements. If a State certificate is issued, the applicant is not permitted to operate vehicles requiring a passenger vehicle or a hazardous materials endorsement.
Colorado	Adopted FMCSA's medical standards to obtain a commercial driver's license. Individuals need to have a medical waiver before they are licensed to drive a commercial vehicle if the individual has a potential disqualifying condition, such as seizures. May be considered to drive taxis, buses, or school bus if the individual provides a physician's certification for treatment and recommendation that provides certainty that the condition is controlled well enough to drive safely.
Connecticut	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers. Not allowed to drive a public service vehicle or service bus with an established medical history or clinical diagnosis of epilepsy or any other condition that results in loss of consciousness or loss of control of a motor vehicle.
Delaware	Adopted FMCSA's medical standards to obtain a commercial driver's license. Individuals not qualifying for a commercial driver's license may file for an intrastate waiver. Not able to drive buses, taxis, or school buses.
District of Columbia	Adopted FMCSA's medical standards to obtain a commercial driver's license. No medical waivers. Not eligible to drive taxis or any public vehicles.
Florida	Adopted FMCSA's medical standards to obtain a commercial driver's license. No medical waivers. Can drive taxis but cannot drive school buses or buses that seat more than 15 people.
Georgia	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers for epilepsy.
Hawaii	Adopted FMCSA's medical standards to obtain a commercial driver's license. Waivers are not available for persons with epilepsy. May drive taxis.
Idaho	To drive a truck in intrastate commerce for exempt commodities (sand, gravel, logs, agricultural products, etc.), same as personal vehicle license. For other types of commodities and other non-exempt commerce, adopted FMCSA's standards. No mention of medical waivers. Individuals with epilepsy may not drive school buses or service buses but may drive taxis.
Illinois	Adopted FMCSA's medical standards to obtain a commercial driver's license. No medical waivers. Cannot drive school buses or service buses carrying more than 16 individuals.
Indiana	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers. May drive taxis, buses, or school buses if the requirements for a personal vehicle license are passed. School bus drivers are required to be free from any mental, nervous, organic or functional disease which might impair their ability to properly operate a school bus.

State	State commercial driving requirements
Iowa	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers. Individuals with epilepsy are not eligible to drive school buses.
Kansas	Adopted FMCSA's medical standards to obtain a commercial driver's license. Waivers may be available.
Kentucky	Adopted FMCSA's medical standards to obtain a commercial driver's license. Individuals with epilepsy may file for a waiver if they have been free of seizures for one year, reliable in taking prescription medications, and have a clear driving record for the last 2 years. Eligible to drive taxis and buses. However, school bus drivers must undergo medical examinations annually.
Louisiana	Adopted FMCSA's medical standards to obtain a commercial driver's license. Medical waivers are not available for people with epilepsy. May obtain a chauffeur's license to transport less than 16 people.
Maine	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers. Individuals with seizures must obtain a School Bus Endorsement to drive a school bus carrying 10 or more passengers.
Maryland	Adopted FMCSA's medical standards to obtain a commercial driver's license. No medical waiver for epilepsy. Not qualified to drive school buses.
Massachusetts	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers. People with a current diagnosis of epilepsy may be eligible to drive school buses.
Michigan	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers. People with epilepsy may obtain a chauffer's license or endorsement to operate a truck or bus if they have been seizure-free for at least 1 year. Not eligible to drive school buses.
Minnesota	Adopted FMCSA's medical standards to obtain a commercial driver's license. No medical waiver for epilepsy.
Mississippi	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waiver for epilepsy. Individuals who meet seizure-free criteria are eligible to drive vehicles that transport passengers.
Missouri	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waiver.
Montana	A driver must a) meet FMCSA's requirements or b) State requirements, which for epilepsy require 5 years seizure-free and a physician finding neither the epilepsy nor medication will affect the ability to drive.
Nebraska	Adopted FMCSA's medical standards to obtain a commercial driver's license for intrastate non-excepted commerce. No mention of medical waivers. For intrastate excepted and interstate excepted commerce, applicants must meet State requirements that allow certification if there has been no seizure in the prior 3 months. Individuals must meet the FMCSA medical standards to drive a school bus.
Nevada	Adopted FMCSA's medical standards to obtain a commercial driver's license. Waivers can be obtained if the individual has been seizure-free for one year. Individuals may transport passengers or hazardous materials if they have been seizure free for 3 years.
New Hampshire	Adopted FMCSA's medical standards to obtain a commercial driver's license. No medical waivers for epilepsy.
New Jersey	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers.
New Mexico	Adopted FMCSA's medical standards to obtain a commercial driver's license. No medical waivers issued.
New York	Adopted FMCSA's medical standards to obtain a commercial driver's license. No medical waivers. Individuals with conditions that cause loss of consciousness are not qualified to drive a school bus.

State	State commercial driving requirements
North Carolina	Adopted FMCSA's medical standards to obtain a commercial driver's license. No waiver for epilepsy.
North Dakota	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waiver for epilepsy. Bus and school bus drivers must meet commercial driver's license requirements.
Ohio	Adopted FMCSA's medical standards to obtain a commercial driver's license. May be eligible for an intrastate waiver. Individuals who have medical history or clinical diagnosis of seizure are not eligible to drive a school bus.
Oklahoma	Adopted FMCSA's medical standards to obtain a commercial driver's license. Waiver may be available if individual is seizure-free for a 5-year period and has a normal examination and EEG. Cannot operate a school bus or commercial vehicle transporting passengers or dangerous or hazardous materials.
Oregon	Adopted FMCSA's medical standards to obtain a commercial driver's license. Individuals with seizure conditions may apply for a medical waiver. School bus drivers have requirements set out by the State Department of Education.
Pennsylvania	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers, except waivers may be available for individuals to drive a school bus.
Rhode Island	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers.
South Carolina	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers.
South Dakota	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waiver for epilepsy. Individuals must meet the FMCSA medical standards to drive a school bus.
Tennessee	Adopted FMCSA's medical standards to obtain a commercial driver's license. Medical waivers are not available for epilepsy.
Texas	Adopted FMCSA's medical standards to obtain a commercial driver's license. Individuals with epilepsy may not obtain a medical waiver.
Utah	Adopted FMCSA's medical standards to obtain a commercial driver's license. Waivers are available for several conditions, including seizures.
Vermont	Adopted FMCSA's medical standards to obtain a commercial driver's license with modifications, including for epilepsy. Certification for epilepsy is on an individual basis.
Virginia	Adopted FMCSA's medical standards to obtain a commercial driver's license. Medical waivers are available for individuals with epilepsy.
Washington	Adopted FMCSA's medical standards to obtain a commercial driver's license. Individuals with epilepsy may apply for a waiver.
West Virginia	Adopted FMCSA's medical standards to obtain a commercial driver's license. If seizure-free for 3 years, the individual may be eligible for a medical waiver.
Wisconsin	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waiver for epilepsy.
Wyoming	Adopted FMCSA's medical standards to obtain a commercial driver's license. No mention of medical waivers.

Table 5. Seizure-free periods prior to licensing for select countries (not exclusive to CMV licensing).

Country	Seizure-free period
Andorra	Must be seizure free for 2 years.
Argentina	No specific regulations. Physicians can advise what a patient should do.
Australia	Laws vary by territory and the seizure-free period ranges from 3 months to 2 years.
Austria	Typically, the period an individual must go seizure free is 2 years but can be extended to 3 years.
Belgium	Depending on the type of seizure, the seizure-free period can be anywhere from 1 to 2 years.
Bulgaria	Individuals who experience seizures cannot drive.
Canada	Varies by province. The typical seizure-free period is 1 year. For commercial driving requirements, see Chapter 17, National Safety Code Standard 6 at the following link: https://ccmta.ca/web/default/files/PDF/National%20Safety%20Code%20Standard%206%20-%20Determining%20Fitness%20to%20Drive%20in%20Canada%20-%20February%202021%20-%20Final.pdf
Central African Republic	Individuals who experience seizures cannot drive.
China	Individuals who experience seizures cannot drive.
Denmark	National Health Board determines the length of time an individual must go seizure free. The typical time length is 2 years.
Egypt	Must be seizure free for 2 years.
Estonia	Individuals who experience seizures cannot drive.
France	An individual must be seizure free for 2 years, but this can be reduced by a physician.
Germany	Individuals who have seizures and are not involved in any sort of motor vehicle accident are not disqualified from driving. For individuals who have seizures and are involved in any sort of motor vehicle accident, the seizure-free period is 2 years.
Ghana	Individuals who experience seizures cannot drive.
Greece	Must be seizure free for 2 years.
Guatemala	Must be seizure free for at least 6 months.
Iceland	Must be seizure free for 2 years.
India	Individuals who have seizures cannot drive.
Ireland	The typical amount of time to wait is between 1 and 2 years.
Israel	For private vehicles, individuals must go 1 year seizure free.
Italy	The regional board decides on the seizure-free period.
Japan	Physicians are required to report which patients can and cannot drive. The seizure-free period is 2 years.
Luxembourg	Must be seizure free for 2 years.
Malaysia	Must be seizure free for 2 years.
Mexico	The amount of time an individual must go seizure free varies by State.
New Zealand	The seizure free period is 1 year but can be reduced to 6 months with the New Zealand Transport Agency's permission and permission from a physician.
Norway	The seizure-free period is 2 years but can be reduced on a case-to-case basis.
Pakistan	Medical examination is required before a license is given to any individual. If an individual has seizures, there is a possibility the individual will not be allowed to drive. No set seizure-free period.
Russia	Individuals who experience seizures cannot drive.
Rwanda	Individuals who experience seizures cannot drive.
Singapore	Individuals who experience seizures cannot drive.

Country	Seizure-free period
Slovenia	Must be seizure free for 2 years.
South Africa	Must be seizure free for 2 years.
South Korea	Typically, people are not allowed to drive unless they are deemed “cured” from epilepsy, but physicians can allow driving after 2 years.
Spain	Must be seizure free for 2 years.
Sri Lanka	Must be seizure free for 3 years.
Sweden	Must be seizure free for 5 years.
Taiwan	Individuals who have had seizures are prohibited from driving.
Turkey	Individuals with epilepsy are not allowed to drive.
United Kingdom	If someone is changing antiepileptic drugs, they can have their license revoked for 6 months. Individuals must report their epilepsy to the Driver and Vehicle Licensing Agency that can determine if the individual needs to go seizure free. Typically, the seizure-free period is 1 year.
Uruguay	Does not have a specific amount of time seizure free.
Uzbekistan	Individuals who experience seizures cannot drive.
European Union (Recommendations)	Recommendations for seizure-free periods: after the first seizure 6 months, for a diagnosis of epilepsy 12 months, a provoked seizure varies, sleep seizures 12 months, and seizure due to change of medication 3 months.

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APPENDIX G: SLEEP EPILEPSY AND SEIZURE RECURRENCE RISKS

Author, Year Score: 3*	D'Alessandro, 2004, Neurology; Unprovoked; Treated/Untreated Title: Risk of seizures while awake in pure sleep epilepsies. Seizure Types: Tonic-clonic seizures.
Category	Seizure, sleep epilepsy
Study Type	Prospective study
Conflict of Interest	Sponsored by Ministry for Universities and Scientific and Technological Research. No mention of COI.
Sample Size	N = 161 with generalized tonic-clonic seizures.
Age/Sex	Mean age: 39.2 years, ranges were 5 patients between 11−15, 24 between 16−20, 56 between 21−40, 33 between 41−60, and 42 over 60. 103 males, 58 females.
Comparison	Following patients to see if their sleep epilepsies will change to awake epilepsy vs. the number of patients who did not have any seizures while awake. All patients were given therapy according to preferences of the patient.
Follow-Up	Follow-up occurred between 24 and 72 months.
Results	Out of all the patients, 18 were recorded as having a seizure while awake and no awake seizures were reported after 55 months of follow-up. The risk of having a seizure while awake after 6 years was 13% (95% CI 7 to 18%). Therapy withdrawal suddenly ($p < 0.001$, hazard ratio = 31.0, 95% CI 1.5–83.8) and seizure frequency were significant ($p = 0.0043$, hazard ratio = 5.77, 95% CI 1.74–19.32).
Conclusion	"In contrast with others, we did not find that a longer duration of sleep epilepsy was associated with a higher risk of seizures while awake. However, the previous studies did not do a multivariate analysis and therefore they may have selected a group of patients with both higher frequency and longer history and therefore with a resistant epilepsy. In our study, pure sleep epilepsies were characterized by a predominance of GTCS, rare occurrence of seizures, and a generally good prognosis, as shown in both humans and kindled animals."
Comments	None

Author, Year Score: 2*	D'Alessandro, 1983, Prog Clin Biol Res; Unprovoked; Untreated Title: Pure sleep epilepsies: Prognostic features. Seizure Types: Sleep epilepsy.
Category	Seizure
Study Type	Observation
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 1,200 patients who had one or more epileptic seizures while sleeping.
Age/Sex	No mention of age or sex.
Comparison	Sleep-related: Frequency of sleep-related epileptic episodes were measured vs. Not Sleep related: Frequency of non-sleep related epileptic episodes were measured.
Follow-Up	No mention of follow-up.
Results	Frequency of sleep-related primary grand mal seizures was 48/1,200 compared to 145/1,200 non-sleep related primary grand mal seizures. Frequency of sleep-related focal grand mal seizures was 29/1,200 compared to 176/1,200 non-sleep related focal grand mal seizures.

Conclusion	"…we have two approaches to the problem of pure sleep epilepsies: at first, theoretical, is to try to understand the physio pathological mechanisms that link sleep and epilepsies; the second, practical, is to examine them from an electroclinical as well as a prognostic point of view."
Comments	Data suggest increased non-sleep related seizures in a large case series.

Author, Year Score: 2*	Fernandez, 2007, Neurology; Unprovoked; Untreated Title: Pure sleep seizures: Risk of seizures while awake. Seizure Types: Sleep epilepsy.
Category	Seizure
Study Type	Retrospective
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 55 patients with pure sleep epilepsy.
Age/Sex	Mean age: 52.6 years, range 18-88. 33 males, 22 females.
Comparison	Frequency of pure sleep seizures were measured over a period of 10 years.
Follow-Up	Follow-up at 10 years.
Results	Seizure frequency was less than 1 per year in 65.5% of patients; 1–10 per year in 14.5% of patients; less than 1 per month in 9.1% of patients. 30.9% of patients (17) had one or more seizure occurrences while awake.
Conclusion	"In spite of a small number of seizures and good response to monotherapy, a third of the patients studied suffered seizures while awake. The significant risk factors were sudden withdrawal of treatment and polytherapy."
Comments	None

Author, Year Score: N/A	Provini, 1999, Brain; Epilepsy Title: Nocturnal frontal lobe epilepsy. Seizure Types: Not specified.
Category	Seizure, nocturnal frontal lobe epilepsy (NFLE)
Study Type	Consecutive Case Series
Conflict of Interest	No mention of sponsorship or COI.
Sample Size	N = 100 patients with NFLE (sleep epilepsy).
Age/Sex	Mean age: 26.3 years. 70 males, 30 females.
Comparison	Patients with paroxysmal arousal (n = 9) vs. patients with nocturnal paroxysmal dystonia (n = 51) vs. patients with episodic nocturnal wanderings (n = 40).
Follow-Up	Follow-up between 1 and 23 years.
Results	The age of onset for nocturnal seizures varies but are mainly seen in infancy. Of all patients, 25% had familial recurrence of the epileptic attacks and 39% of patients have family history of the nocturnal epileptic episodes. In most patients, ictal (44%) and the interictal (51%) EEGs were uninformative.
Conclusion	"Its clinical relevance has been and still is underestimated, and many cases, especially in children, are misdiagnosed as arousal disorders. NFLE is, however, heterogeneous, and [autosomal dominant nocturnal frontal lobe epilepsy] is a genetic variant which is itself both clinically and biologically heterogeneous. NFLE is not always a benign condition, many patients being resistant to any antiepileptic drug therapy."
Comments	Study of sleep epilepsy

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