Expert Panel Recommendations
Seizure Disorders and Commercial Motor Vehicle Driver Safety

Medical Expert Panel Members

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Federal Motor Carrier Safety Administration will consider all Medical Review Board and Medical Expert Panel recommendations, however, all proposed changes to current standards and guidance (guidelines) will be subject to public-notice-and-comment and relevant rulemaking processes.

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Introduction

The primary mission of the U.S. Department of Transportation's (DOT's) Federal Motor Carrier Safety Administration (FMCSA) is to reduce crashes, injuries and fatalities involving commercial motor vehicles (CMVs), including large trucks and buses. One mechanism used to facilitate this effort is the updating of current, and the development of new, medical fitness standards for drivers of CMVs and guidelines for medical examiners. FMCSA is committed to review and begin updating all of their current standards and guidelines by 2009.

This report serves the purpose of summarizing the considerations and recommendations of a panel of experts in the field of neurology (henceforth termed the Medical Expert Panel (MEP)) who examined FMCSA's current guidelines for medical examiners pertaining to seizure disorders.

Guideline Development Personnel

Members of the MEP charged with making recommendations pertaining to whether the current guidelines for seizure disorders need to be updated are listed in Table 1.

Table 1. Members of the MEP

Name	Current Position
Jerome "Pete" Engel, Jr., MD, PhD	Professor, Neurology and Neurobiology Director; Epilepsy Telemetry Unit, Seizure Disorder Center, Adult Epilepsy University of California Los Angeles
Robert S. Fisher, MD, PhD	Maslah Saul MD Professor of Neurology Director, Stanford Comprehensive Epilepsy Center Stanford University School of Medicine
Gregory L. Krauss, MD	Associate Professor of Neurology Director, Adult Epilepsy Clinic The Johns Hopkins University School of Medicine
Allan Krumholz, MD	Professor of Neurology Director, Maryland Epilepsy Center University of Maryland
Mark S. Quigg, MD	Assistant Professor of Neurology Director, EEG/Intensive Monitoring/Evoked Potential Laboratories University of Virginia

Methodology

Brief Overview of Evidence Report Methodology

The recommendations contained in this report are based in part upon the interpretation and assimilation of information presented in a comprehensive systematic review of available literature, prepared by ECRI Institute and Manila, and presented to the MEP on May 14, 2007. The evidence report was developed following a systematic literature search for evidence accessible from seven electronic databases — Medline, PubMed (pre Medline), EMBASE, PsycINFO, CINAHL, TRIS, and the Cochrane Library (through February 5, 2007). Additional hand searches of the published literature (i.e., bibliographies of identified relevant articles), and "gray literature" resources (e.g., Web searches) were also performed.

Data obtained from these searches were screened against a set of a priori inclusion criteria. Included data were pooled and synthesized, where applicable, using meta-analytic techniques described in detail in the Evidence Report titled, "Seizure Disorders and Commercial Motor Vehicle Driver Safety." See also Appendix B of this report.

Pre-Meeting Preparation

Thirty days prior to the MEP meeting, each member of the panel was provided with a draft copy of the aforementioned Evidence Report. Panel members were also provided with a guideline workbook. This workbook consisted of two separate worksheets highlighting FMCSA's current guideline recommendations for medical examiners on the certification and recertification of individuals who have experienced (or are at risk for experiencing) a seizure (see Appendix A). The topics covered by the current guidelines included the following:

- Unprovoked seizures.
- Insults to the nervous system that provoked a seizure.
- Insults to the nervous system that did not provoke a seizure but which represent a risk for future seizures.

Members of the panel were asked to review the existing guideline recommendations, in conjunction with their review of current information presented in the companion Evidence Report, to determine whether existing recommendations required updating. More specifically, panel members were instructed to determine:

1. Whether each of the existing guidelines is acceptable.
2. If not acceptable, to provide an explanation as to why.
3. If not acceptable, to provide suggested changes to the existing guideline.
4. If a suggested change is proposed, to state whether this change is supported with evidence.
5. If evidence exists, to provide citations for this evidence.

The MEP Meeting and Recommendation Formulation

On May 14, 2007, FMCSA, Manila, ECRI Institute, and members of the MEP convened a two day conference. The purpose of this conference was several-fold:

- To review the existing FMCSA guidelines for medical examiners which pertain to the certification and recertification of individuals who have either experienced, or who are at risk for experiencing a seizure.
- To discuss the available evidence contained in the Evidence Report and other sources pertaining to the consequences to public safety associated with allowing individuals who have either experienced, or who are at risk for experiencing a seizure, to drive a CMV.
- To recommend changes to the existing FMCSA guidelines which are deemed necessary following the critical assessment of the available evidence.

In developing recommendations to FMCSA, members of the panel were guided by three central principles. These principles were as follows:

- Recommended changes to the existing FMCSA guidelines should be based on scientific evidence whenever possible[1].
- Recommended changes to the existing FMCSA guidelines should be concise and explicit.
- Recommended changes to the existing FMCSA guidelines should be actionable.

This document reflects a summary of the recommendations derived from this consensus process.

Recommended Changes to Original Guidelines

The MEP recommended that FMCSA make substantial changes to the current seizure disorder guidelines. These recommendations were based on a combination of evidence provided by the Evidence Report titled, "Seizure Disorders and Commercial Motor Vehicle Driver Safety" and other sources. Below we present the recommendations of the MEP and provide justification for these recommendations.

Guideline 1: Fitness-to-drive certification of individuals with a history of epilepsy

The MEP recommended that the current guidelines pertaining to individuals who have a diagnosis of epilepsy (Appendix A) be replaced with the following:

- A history of epilepsy precludes an individual from obtaining unconditional certification to drive a CMV for the purposes of interstate commerce.
- A history of epilepsy, however, should not unconditionally exclude all individuals from driving a CMV; conditional certification may be possible in some instances.
- An individual with a history of epilepsy may obtain conditional certification (or maintaining certification under conditional status) to drive a CMV if that individual meets the following criteria:
  - Individual must have been seizure free for a minimum of 8 years on or off anti-seizure medication; **AND**
    - If all anti-seizure medications have been stopped, the individual must have been seizure free for a minimum of 8 years from the time of medication cessation; **OR**
    - If still using anti-seizure medication, the individual must have been on a stable medication regimen for a minimum of 2 years.
- An individual with a history of epilepsy who has been granted conditional certification to drive a CMV must be recertified on an annual basis.

[1] Recommendations from the MEP, for which no supporting evidence was identified and which are thus based on expert opinion alone, are identified as such.

Justification: *The MEP referenced three sources in support of Guideline 1 (see Evidence Sources below). The MEP deemed an annual seizure risk of 2% to be an acceptable threshold below which an individual may be considered fit to drive a CMV. Note that this 2% upper limit of ensures that the annual risk for experiencing a seizure while driving will be less than 0.5% (assuming a 50 hour work week). The choice of 2% as the upper limit of acceptable risk is in agreement with the position of several other organizations including the previous MEP, the European Union, the Australian National Transportation Commission, and the United Kingdom Department of Motor Vehicles. For professional air-crew in Europe (professional aircrew require Class 1 medical certification), an annual risk for incapacitation of less than 1% is deemed to be acceptable provided that the pilot is working in a multi-crew environment. Thus, in Europe, individuals who have been seizure free for 10 years or longer and who have been off seizure medication for at least two years may obtain Class 1 certification with a multi-crew restriction.*

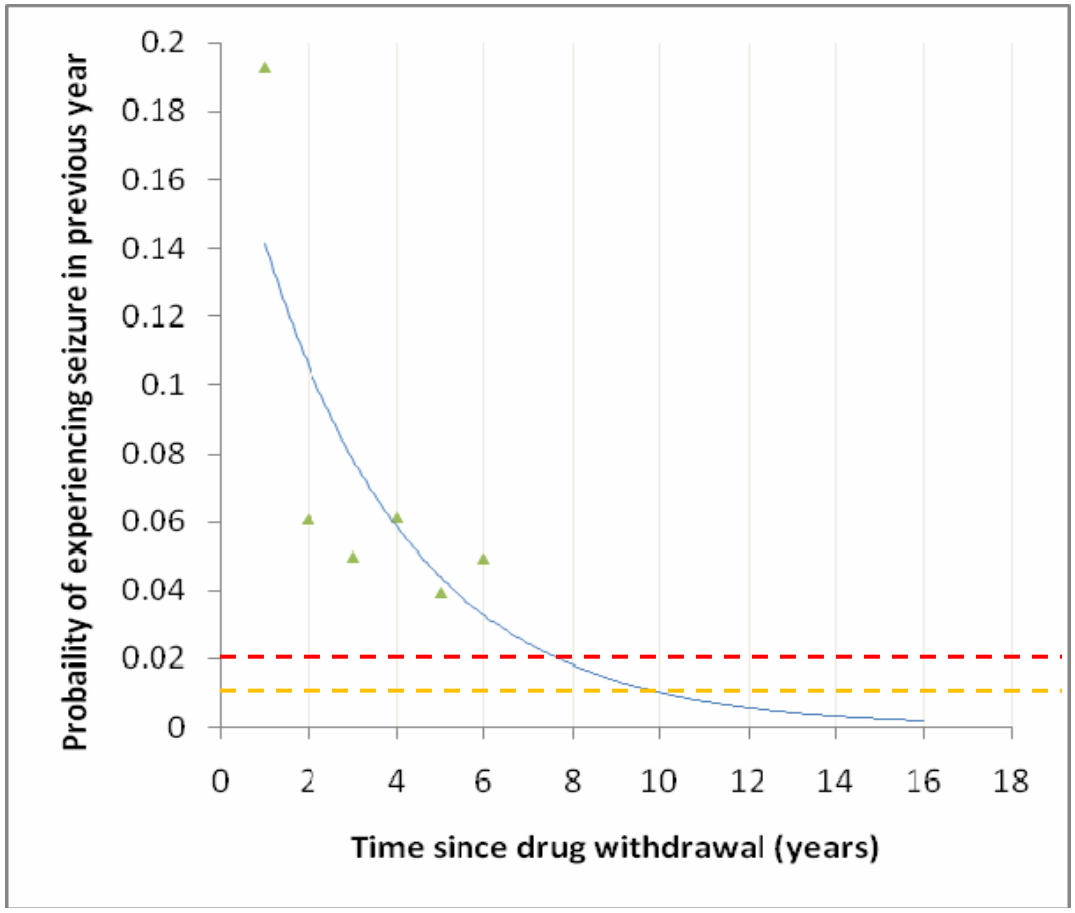
The authors of the FMCSA Evidence Report did not identify any studies that provide direct evidence pertaining to the risk of seizure recurrence among individuals who are seizure free while being treated long-term with AEDs. The Evidence Report did provide evidence pertaining to seizure recurrence rates following surgery. A meta-analysis of these data found that the annual seizure recurrence rate among individuals who have been seizure free for a minimum of 8 years following surgery is less than 2%. It is not clear whether the results of this analysis can be generalized to individuals who have not undergone surgery.

Chadwick et al. (1996) reported that seizure recurrence among individuals who had undergone AED withdrawal was most likely to occur during the first two post-withdrawal years (Table 2).While Chadwick et al. only reported seizure recurrence data out to 5 years post drug withdrawal ,the MEP fitted the data using the same techniques described in the evidence report (assuming an exponential probability distribution) and used extrapolation to estimate the time pont at which seizure recurrence rates would fall below 2% (Figure 1).Using this method the MEP calculated that the 2% annual seizure risk level would be attained approximately 8 years after AED withdrawal and the 1% risk level would be attained approximately 10 years following withdrawal.

Table 2. Number of individuals at risk, with seizures, and hazard ratios with time (from Chadwick et al.[1996])

	Number of seizures (number at risk)					
Time since drug withdrawal	0 to 1 yrs	1 to 2 yrs	2 to 3 yrs	3 to 4 yrs	4 to 5 yrs	5 to 6 yrs
Carbamazepine	35 (237)	46 (202)	56 (190)	67 (178)	73 (157)	76 (115)
Phenytoin	51 (184)	55 (131)	59 (126)	65 (121)	69 (111)	75 (87)
Sodium valproate	42 (228)	57 (185)	69 (170)	82 (155)	89 (136)	94 (103)
PB/PR	11 (72)	16 (59)	17 (54)	18 (53)	19 (51)	22 (39)
Any drug	139 (721)	174 (577)	201 (540)	232 (507)	250 (455)	267 (344)

Figure 1. Probability of experiencing seizure in previous year as a function of time since drug withdrawal



Given the data from Chadwick et al. and the findings of their analysis, the MEP decided upon the Guidelines listed above. A 2% risk of recurrence at 8 years for an individual who had been seizure free for a minimum of 8 years, whether using or having discontinued the use of AEDs, was an appropriate amount of risk, and an appropriate amount of time to wait, to achieve certification of medical fitness to drive. This decision was made with the proviso that individuals who had discontinued AED use had to have a minimum of 8 years without seizures post-AED withdrawal or, that individuals who were still receiving AED therapy must be on a stable pharmacotherapeutics regimen and have been seizure free for a minimum of 2 years. Any seizure within the previous 8 years would disqualify that individual from achieving medical certification to drive a CMV until such time as the time limit imposed had been satisfied.

Evidence Sources:

- Australian NTC - Assessing Fitness to Drive - Austroads Interim Report 2005: http://www.austroads.com.au/aftd/index.html (see page 55).
- Carter T. Fitness Standards for the Transportation Industries. J R Soc Med 2001; 94: 534-535.
- Chadwick D, Taylor J, Johnson T. Outcomes after seizure recurrence in people with well-controlled epilepsy and the factors that influence it. The MRC Antiepileptic Drug Withdrawal Group. Epilepsia 1996 Nov;37(11):1043-50.
- Conference on Neurological Disorders and Commercial Drivers - FHWA-MC-88-042, July 1988 (see: http://www.fmcsa.dot.gov/documents/neuro.pdf).
- Johnston RV, O'Brien, MD. Neurological Disease at 30 000 Feet –What is an Acceptable Risk for your Pilot? *Practical Neurology* 2004;4;322-325.
- Medical Aspects of Fitness to Drive. Commission on Accident Prevention. 5th edn. London: MCAP 1995: 61-82.
- Minutes of the Secretary of State's Honorary Medical Advisory Panel on Driving and Disorders of the Nervous System held on 27th October 2004.
- Minutes of the Secretary of State's Honorary Medical Advisory Panel on Driving and Disorders of the Nervous System held on 19th October 2005.
- Spencer MB. Risk analysis and fitness to drive: an evaluation of sensitivity issues - Road Safety Research Report No. 41. United Kingdom Department of Transport (2003).
- Second European Working Group on Epilepsy and Driving, an advisory board to the Driving License Committee of the European Union. Epilepsy and Driving in Europe. Final Report April 2005.
- Tiller M, Tregear SJ, Price N, et al. Seizure Disorders and Commercial Motor Vehicle Driver Safety – Evidence Report. Prepared by Manila Consulting Incorporated and the ECRI Institute for FMCSA (In Press).

Guideline 2: Fitness-to-drive certification of individuals with a history of a single unprovoked seizure

The MEP recommended that the current guideline pertaining to individuals who have experienced a single, unprovoked seizure (Appendix A) be replaced with the following guideline:

- A history of experiencing a single unprovoked seizure precludes an individual from obtaining unconditional certification to drive a CMV for the purposes of interstate commerce.
- A history of experiencing a single unprovoked seizure, however, should not unconditionally exclude all individuals from driving a CMV; conditional certification may be possible in some instances.

- An individual with a history of a single, unprovoked seizure may obtain conditional certification (or maintaining certification under conditional status) to drive a CMV if that individual meets the following criteria:
  - Individual must have been seizure free for a minimum of 4 years on or off anti-seizure medication; **AND**
    - If all anti-seizure medications have been stopped, the individual must have been seizure free for a minimum of 4 years from the time of medication cessation; **OR**
    - If still using anti-seizure medication, the individual must have been on a stable medication regimen for a minimum of 2 years.
- An individual with a history of a single, unprovoked seizure who has been granted conditional certification to drive a CMV must be recertified on a biennial basis.

Justification for change: *Panel members objected to holding individuals with a solitary unprovoked seizure to the same regulations as individuals who had been diagnosed with epilepsy. It was ultimately decided that individuals who had suffered a solitary seizure should be eligible to apply for medical certification to drive a CMV after a minimum of 4 years on or off AED therapy provided that the individual who had stopped AED therapy had been seizure free for minimum of 4 years post-withdrawal. In the 'absence of any data', it was decided that individuals who were still utilizing AEDs must be on a stable pharmacotherapeutics regimen for 2 years.*

The findings of a meta-analysis of data from four studies included in the FMCSA Evidence Report titled, " Unprovoked Seizures and Commercial Motor Vehicle Driver Safety," found that individuals who have been seizure free for a period of four or more years following a single unprovoked seizure have an annual risk of ≤2% for seizure recurrence.

Evidence Sources:

- Berg AT, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. Neurology 1991 Jul;41(7):965-72.
- Gilad R, Lampl Y, Gabbay U, Eshel Y, Sarova-Pinhas I. Early treatment of a single generalized tonic-clonic seizure to prevent recurrence. Arch Neurol 1996 Nov;53(11):1149-52.
- Hauser WA, Rich SS, Annegers JF, Anderson VE. Seizure recurrence after a 1st unprovoked seizure: an extended follow-up. Neurology 1990 Aug;40(8):1163-70.
- Hopkins A, Garman A, Clarke C. The first seizure in adult life. Value of clinical features, electroencephalography, and computerised tomographic scanning in prediction of seizure recurrence. Lancet 1988 Apr 2; 1(8588):721-6.
- Kollar B, Buranova D, Goldenberg Z, Klobucnikova K, Varsik P. Solitary epileptic seizure--the risk of recurrence. Neuroendocrinol Lett 2006 Feb-Apr; 27(1-2):16-20.

- Tiller M, Tregear SJ, Price N, et al. Seizure Disorders and Commercial Motor Vehicle Driver Safety – Evidence Report. Prepared by Manila Consulting Incorporated and the ECRI Institute for FMCSA (In Press).
- Van Donselaar CA, Geerts AT, Schimsheimer R-J. Idiopathic first seizure in adult life: Who should be treated? BMJ 1991; 302(6777):620-3.

Guideline 3: Fitness-to-drive certification of individuals with a history of a provoked seizure or seizures;

This category of seizure pertains to a provoked seizure. Certification may be allowed if the individual is at low risk for again encountering the factor that precipitated the seizure or of having further seizures. Patients whose seizures are provoked by sleep deprivation, photic or visual pattern stimulation will not be considered for certification under this guideline, since these patients may have underlying epilepsy. Conditional certification of such individuals will be considered according to Guideline 1. The MEP recommended that the current guideline pertaining to individuals who have experienced a symptomatic seizure or seizures (Appendix A) be replaced with the following guideline:

- A history of experiencing a single provoked seizure should not automatically preclude an individual from obtaining unconditional certification to drive a CMV for the purposes of interstate commerce.
- Whether an individual with such a history can be unconditionally certified requires an individual evaluation to ascertain that the individual is at a sufficiently low recurrence risk for again encountering the factor that precipitated the seizure or of having further seizures.
- Examples of low risk for recurrence include:
  - A lidocaine-induced seizure during a dental appointment.
  - A concussive seizure, loss of consciousness ≤30 minutes, no penetrating injury.
  - A seizure due to syncope not likely to recur while driving.
  - A seizure from an acute metabolic derangement not likely to recur.
  - Drug withdrawal.

Conditional certification may be considered for individuals with moderate-to-high risk factors for recurrence provided that the following conditions are met:

- Individual must have been seizure free for a minimum of 8 years on or off anti-seizure medication; **AND**
  - If all anti-seizure medications have been stopped, the individual must have been seizure free for a minimum of 8 years from the time of medication cessation; **OR**
  - If still using anti-seizure medication, the individual must have been on a stable medication regimen for a minimum of 2 years.
- An individual with a history of epilepsy who has been granted conditional certification to drive a CMV must be recertified on an annual basis.

- Examples of seizure-provoking conditions that are at moderate-to-high risk for further seizures, and therefore would weigh against certification, include the following:
  - Head injury with loss of consciousness or amnesia ≥ 30 minutes or penetrating head injury.
  - Intracerebral hemorrhage of any etiology, including stroke and trauma.
  - Brain infection: encephalitis, meningitis, abscess, cysticercosis.
  - Stroke.
  - Intracranial hemorrhage.
  - Post-operative brain surgery with significant brain hemorrhage.
  - Brain tumor.

Justification for change: *Panel members posited that acute symptomatic seizures should be divided into those with ongoing risk factors and without ongoing risk factors. When the provocative agent is at low risk to recur (ex. seizure associated with the administration of lidocaine) and exposure to the agent is known not to be associated with an enduring, potentially epileptogenic lesion, this should not provide a barrier to applying for medical certification to drive a CMV. When the provocative agent is an ongoing risk factor (seizure associated with stroke) then there should be additional consideration as to the ability to certify the individual to operate a CMV.*

Evidence Sources:

- See Appendix D.

APPENDIX A: Current FMCSA Standards and Guidelines for Medical Examiners Pertaining to Seizure Disorders

Appendix A summarizes the FMCSA's current standards and guidelines pertaining to individuals with seizure disorders.

Current United States Federal Regulatory and Medical Advisory Criteria for CMV Operators

FMCSA Regulations, found in 49 Code of Federal Regulations (CFR) 301 through 399, cover businesses that operate CMVs in interstate commerce. FMCSA regulations that pertain to fitness to drive a CMV are found in 49 CFR 391 Subpart E. Only motor carriers engaged purely in intrastate commerce are not directly subject to these regulations. However, intrastate motor carriers are subject to State regulations, which must be identical to, or compatible with, the Federal regulations in order for States to receive motor carrier safety grants from FMCSA. States have the option of exempting CMVs with a gross vehicle weight rating of less than 26,001 lb.

49 CFR 391 Subpart E—Physical Qualifications and Examinations

49 CFR 391 Subpart E states the following:

(a) A person shall not drive a CMV unless he/she is physically qualified to do so and, except as provided in §391.67, has on his/her person the original, or a photographic copy, of a medical examiner's certificate that he/she is physically qualified to drive a CMV.

(b)(8) 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 CMV;

Epilepsy is a chronic functional disease characterized by seizures or episodes that occur without warning, resulting in loss of voluntary control which may lead to loss of consciousness and/or seizures. Therefore, the following drivers cannot be qualified:

(1) a driver who has a medical history of epilepsy;
(2) a driver who has a current clinical diagnosis of epilepsy; or
(3) a driver who is taking antiseizure medication.

If an individual has had a sudden episode of a non-epileptic seizure or loss of consciousness of unknown cause which did not require antiseizure medication, the decision as to whether that person's condition will likely cause the loss of consciousness or loss of ability to control a CMV is made on an individual basis by the medical examiner in consultation with the treating physician. Before certification is considered, it is suggested that a 6-month waiting period elapse from the time of the episode. Following the waiting period, it is suggested that the individual have a complete neurological examination. If the results of the examination are negative and antiseizure medication is not required, then the driver may be qualified.

In those individual cases where a driver had a seizure or an episode of loss of consciousness that resulted from a known medical condition (e.g., drug reaction, high temperature, acute infectious disease, dehydration, or acute metabolic disturbance), certification should be deferred until the driver has fully recovered from that condition, has no existing residual complications, and is not taking antiseizure medication.

Drivers with a history of epilepsy/seizures who are off antiseizure medication and who have been seizure-free for 10 years may be qualified to operate a CMV in interstate commerce. Interstate drivers with a history of a single unprovoked seizure may be qualified to drive a CMV in interstate commerce if seizure-free and off antiseizure medication for a 5-year period or more.

More extensive information on this topic is available at the *Conference on Neurological Disorders and Commercial Drivers* at: http://www.fmcsa.dot.gov/rulesregs/medreports.htm

APPENDIX B: Findings of Evidence Report

This appendix summarizes the findings of the Evidence Report titled, "Seizure Disorders and Commercial Motor Vehicle Safety." The purpose of the evidence report was to address several key questions posed by FMCSA. FMCSA developed each of these key questions so that the answers will provide information useful in updating its current medical examination guidelines. The six key questions addressed in the evidence report were:

Key Question 1: Are individuals with seizure disorders (epilepsy) at an increased risk for a motor vehicle crash when compared with comparable individuals who do not have seizure disorder?

Key Question 2: What is the relationship between seizure recurrence likelihood and the time since last seizure among individuals who are on AED treatment and are apparently seizure free?

Key Question 3: What is the relationship between seizure recurrence likelihood and the time since last seizure among individuals who have undergone surgery and are apparently seizure free?

Key Question 4: What is the relationship between seizure recurrence likelihood and the time since last seizure among individuals who have experienced a single unprovoked seizure?

Key Question 5: What is the relationship between treatment compliance (as measured by drug serum levels) and treatment effectiveness?

Key Question 6: What are the chronic[2] effects of an AED on surrogate markers of driver safety among individuals with recurrent seizure disorders? Surrogate markers of driver safety are:

a) Driving performance (simulated or closed course)
b) Cognitive and psychomotor function

Identification of Evidence Bases

Separate evidence bases for each of the key questions addressed by the evidence report were identified using a process consisting of a comprehensive search of the literature, examination of abstracts of identified studies in order to determine which articles would be retrieved, and the selection of the actual articles that would be included in each evidence base.

A total of seven electronic databases (Medline, PubMed (pre Medline), EMBASE, PsycINFO, CINAHL, TRIS, the Cochrane library) were searched (through February 5, 2007). In addition, we examined the reference lists of all obtained articles with the aim of identifying relevant articles not identified by our electronic searches. Hand searches of the "gray literature" were also performed. Admission of an article into an evidence base was determined by formal retrieval and inclusion criteria that were determined *a priori.*

[2] >2 weeks treatment

Grading the Strength of Evidence

Our assessment of the quality of the evidence took into account not only the quality of the individual studies that comprise the evidence base for each key question; we also considered the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Analytic Methods

The set of analytic techniques used in this evidence report was extensive. Random- and fixed-effects meta-analyses were used to pool data from different studies.(1-5) Differences in the findings of studies (heterogeneity) were identified using the Q-statistic and I^2.(6-8) Sensitivity analyses, aimed at testing the robustness of our findings, included the use of cumulative fixed- and random-effects meta-analysis.(9-11) The presence of publication bias was tested for using the "trim and fill" method.(12-14)

Presentation of Findings

In presenting our findings we make a clear distinction between qualitative and quantitative conclusions and we assign a separate strength-of-evidence rating to each type of conclusion format. The strength-of-evidence ratings assigned to these different types of conclusion are defined in Table 3.

Table 3. Strength of Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	*Interpretation*
Qualitative Conclusion	
Strong evidence	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI recommends regular monitoring of the relevant literature for moderate-strength conclusions.
Acceptable	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will either overturn or strengthen our conclusions. ECRI recommends frequent monitoring of the relevant literature.
Unacceptable	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI recommends frequent monitoring of the relevant literature.
Quantitative Conclusion (Stability of Effect Size Estimate)	
Highly stable	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderately stable	The estimate of treatment effect the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends regular monitoring of the relevant literature.
Low stability	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends frequent monitoring of the relevant literature.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI recommends frequent monitoring of the relevant literature.

Findings

The findings of our analyses of the data pertaining to the six key questions addressed in the evidence report are summarized below.

Key Question 1: Are individuals with recurrent seizure disorders (epilepsy) at an increased risk for a motor vehicle crash when compared to comparable individuals who do not have the disorder?

Individuals with epilepsy are more likely (between 1.13 and 2.16 times) to experience a motor vehicle crash than comparable individuals who do not have the disorder (Strength of Evidence: Moderate).

- **Because of unexplained heterogeneity, one cannot determine a single precise estimate of the magnitude of this increased risk (Stability of Point Estimate: Unacceptable).**

Eight included studies (Median Quality=Low) addressed Key Question 1. All eight studies presented data on the ratio of crashes experienced by a group of individuals with epilepsy as compared to a group of individuals who did not have the disorder. Analysis of crash data from the included studies found these data to be inconsistent ($Q=59.59$, $P<0.0001$; $I^2=88.25$). Five included studies found an increased risk associated with epilepsy, one included study found no evidence of an increased crash risk and two included studies found that crash risk was reduced among individuals with epilepsy.

Meta-regression analyses found that one of 11 covariates examined was significantly correlated with outcome; this covariate being whether the study evaluated fatal crashes only. However, this single variable regression model is not adequate to explain a sufficiently large degree of heterogeneity for us to present a single estimate of the crash rate ratio. Pooling the data from the included studies while controlling for the impact of reporting on fatal crashes only using a random effects model found that on average, individuals with epilepsy are more likely (somewhere between 1.13 and 2.13 times) to experience a motor vehicle crash than comparable individuals who do not have the disorder.

Key Question 2: What is the relationship between seizure recurrence likelihood and the time since last seizure among individuals who are on AED treatment and are apparently seizure free?

Because no studies met the inclusion criteria for Key Question 2, we are precluded from developing models for predicting the likelihood that an individual who has been seizure free for a specific period of time will experience seizure recurrence in the near future.

It is established that the cumulative probability that an individual will remain seizure free diminishes as a function of time since last seizure. The purpose of this section of the evidence report was to attempt to model this relationship with the aim of providing a means with which one can determine the likelihood that seizures will recur in the near future (following year) among individuals with epilepsy who have been successfully treated (remained seizure free) with AEDs.

None of the studies identified by our searches fulfilled all the inclusion criteria for this key question. The primary reason for exclusion was that no identified study that included seizure free individuals currently undergoing treatment with an AED treatment reported time since last seizure as an index event. All studies used as an index either: a) time of entry at study; b) time since beginning or accomplishing AED withdrawal (withdrawal studies); c) time since beginning AED therapy (efficacy studies); d) the minimum time seizure free as inclusion criteria, meaning that individuals in the study had varying amounts of seizure free time, none of which were recorded separately.

Key Question 3: What is the relationship between seizure recurrence likelihood and the time since last seizure among individuals who have undergone surgery and are apparently seizure free?

The longer the time that has elapsed since the occurrence of the last seizure in an individual who has undergone surgery for focal epilepsy (primarily temporal lobectomy), the lower the risk for seizure recurrence in the following year (Strength of Evidence: Acceptable).

- **The average annual risk for experiencing seizure recurrence among individuals who have undergone surgery for focal epilepsy and have remained seizure free for ≥8 years is less than 2% (Stability of Estimate: Low).**
- **The average annual risk for experiencing seizure recurrence among individuals who have undergone surgery for focal epilepsy and have remained seizure free for ≥10 years is less than 1% (Stability of Estimate: Low).**

Twelve studies (Median Quality Score=6.25: Low) met the inclusion criteria for Key Question 3. All twelve studies were case series in which data on seizure status, recorded over a period of several years, was analyzed using typical survival (time-to-event) analysis techniques. Data on seizure status was usually drawn retrospectively from medical records (only one study was prospective). Sometimes this information was supplemented by telephone interviews of the patient or a close family member.

All of the included studies were designed to assess the long-term effectiveness and safety of surgery for medically intractable localized epilepsy. The majority of included studies examined the long-term effectiveness of temporal lobectomy; three included studies evaluated the effectiveness of other surgical procedures in addition to temporal lobectomy. Other procedures assessed by these studies included frontal, occipital, and parietal lobectomies. As a consequence, the findings of our analysis are generalizable only to individuals who become seizure free following one of these procedures.

A summary time-to-event (survival) function was determined from relevant data extracted from the 12 included studies using curve fitting software. Time-to-event data from each study was well fit using a non-linear regression model in which the underlying probability distribution was exponential. The hazard function for a survival curve with an exponential probability distribution is described by a single constant, the hazard rate. In order to model a summary time-to-event curve, the hazard rate and its 95 percent confidence intervals determined for each included study. A hazard rate could not be determined for one of the 12 studies because too few data points were available for a curve to be reliably fitted.

Heterogeneity testing of the hazard rate data from the 11 remaining studies were found to be heterogeneous ($Q=137.27$, $P<0.0001$; $I^2=92.72$). This heterogeneity was explored using mixed effects maximum-likelihood meta-regression. Because of the small number of studies included in the evidence base for this question we were precluded from developing meta-regression models that utilized more than one covariate. None of the covariates that could be assessed were found to independently have a significant impact on the risk rate, λ.

Because the observed heterogeneity across the hazard rates could not be explained we pooled these hazard rate data using a random-effects model which incorporated the heterogeneity into the summary estimate of the hazard rate and its confidence intervals. The random-effects summary hazard rate was found to be 0.39 (95 percent confidence interval [CI]: 0.26 to 0.53).

The summary hazard rate and its 95 percent confidence intervals were used to construct a summary time-to-event curve which in turn was used to determine a conservative estimate of the likelihood that a surgically treated individual will experience seizure recurrence within the following year given that they have been seizure free for a specified period of time.

According to guidelines from Austroads an annual seizure risk of 20 percent–50 percent for private license holders and 1 percent–2 percent for commercial drivers are considered acceptable risk levels for allowing an individual to drive. The findings of our model suggest that individuals who have been seizure free for at least eight years following surgery have an annual risk for seizure recurrence of ≤2 percent. Individuals who have been seizure free for at least 10 years following surgery have an annual risk for seizure recurrence of ≤1 percent.

The reader is cautioned that the findings of our analysis are based on data extracted from several low quality studies and that the findings of the model have not been tested in a prospective study. In addition, the reader should note that our findings do not pertain to all individuals who have undergone surgery for epilepsy. Rather, these findings should be limited primarily to individuals who are seizure free following a temporal lobectomy.

Key Question 4: What is the relationship between seizure recurrence likelihood and the time since last seizure among individuals who have experienced a single unprovoked single seizure?

The longer the time that has elapsed since the occurrence of a single unprovoked seizure, the lower the risk for seizure recurrence in the near future (Strength of Evidence: Acceptable).

- **The annual risk for experiencing seizure recurrence among individuals who have experienced a single unprovoked seizure and who have remained seizure free for ≥4 years is less than 2% (Stability of Estimate: Low).**

Key Question 4 focused on a specific population of individuals who had experienced one unprovoked seizure in their lives. A key concern to those involved in road safety is the risk for seizure recurrence following such a seizure. Consequently, we searched for studies of that evaluated the risk for seizure recurrence following an individual's first unprovoked seizure.

Four studies (Median Quality: Low) met the inclusion criteria for Key Question 4. All four studies were case-series in which a group of individuals were followed after the advent of a single unprovoked seizure until seizure recurrence occurred. The time-to-event data observed in these four studies was limited in the length of follow up with only one included study following individuals for more than five years.

A summary time-to-event (survival) function was determined from relevant data extracted from the four included studies using curve fitting software. Time-to-event data from each study was well fit using a non-linear regression model in which the underlying probability distribution was exponential. The hazard function for a survival curve with an exponential probability distribution is described by a single constant, the hazard rate. In order to model a summary time-to-event curve, the hazard rate and its 95 percent confidence intervals determined for each included study.

Heterogeneity testing of the hazard rate data from the four included studies were found to be heterogeneous ($Q=29.38$, $P<0.0001$; $I^2=89.79$). This heterogeneity was explored using mixed effects maximum-likelihood meta-regression. Because of the small number of studies included in the evidence base for this question we were precluded from developing any meta-regression models. Consequently, we pooled these hazard rate data using a random-effects model which incorporated the heterogeneity into the summary estimate of the hazard rate and its confidence intervals. The random-effects summary hazard rate was found to be 0.09 (95 percent CI: 0.04 to 0.13).

The summary hazard rate and its 95 percent confidence intervals were used to construct a summary time-to-event curve which in turn was used to determine a conservative estimate of the likelihood that a surgically treated individual will experience seizure recurrence within the following year given that they have been seizure free for a specified period of time. The findings of our model suggest that individuals who have been seizure free for at least four years following a single unprovoked seizure have an annual risk for seizure recurrence of ≤2 percent.

Key Question 5: What is the relationship between treatment compliance (as measured by drug serum levels) and treatment effectiveness?

Because of inconsistencies in the available evidence, one is precluded from drawing an evidence-based conclusion pertaining to the strength of the relationship between compliance and crash risk at this time.

Five studies met the inclusion criteria for Key Question Five (Median Quality: Low). Only one of these included studies examined the relationship between compliance and crash. This case-control study (Quality: Low) did not find evidence that non-compliance increased crash risk. However, it did find that shorter seizure-free intervals were associated with an increased crash risk (see Key Question 1). The remaining four studies examined the relationship between compliance and seizure frequency. Two of these studies were randomized control trials (RCTs). These RCTs were designed to examine the effectiveness of interventions aimed at improving compliance. The results of these two studies are inconsistent. One of these RCTs (Quality: Moderate) found that compliance education reduced seizure frequency which suggests that better compliance reduces seizure risk. However, the other RCT (Quality: Moderate) did not find such a relationship.

The remaining two studies stratified a cohort of individuals with epilepsy who were on AED therapy into two groups: compliers and non-compliers. Seizure frequency was then compared between the two groups. Again the findings of these studies are inconsistent. One of these studies (Quality: Low) found that seizure frequency was lower among compliers while the other study (Quality: Low) did not.

Because of inconsistencies in the available evidence, one is precluded from drawing an evidence-based conclusion pertaining to the strength of the relationship between compliance (as measured using blood AED serum levels) and crash risk at this time. More data, preferably from studies that have examined the relationship directly, are required before evidence-based conclusions pertaining to the relationship.

Key Question 6: What are the chronic effects of an AED on surrogate markers of driver safety among individuals with recurrent seizure disorders?

Cognitive and psychomotor deficits have been demonstrated in studies of AED use in individuals with epilepsy. However, FMCSA is interested the relationship between AED use and cognitive and psychomotor deficits in a specific group of individuals who might qualify for a CMV drivers license. This subgroup of individuals will be adults (I >18 year of age) with well controlled epilepsy who have been seizure free for a minimum of 6 months. The findings of our analysis of data from studies that enrolled such individuals and that evaluated the impact of AEDs on indirect measures of driving ability are presented below:

1. **A paucity of appropriate data precludes drawing an evidence-based conclusion about the effects of chronic AED treatment on driving performance as measured by a simulator.**

   None of the included studies identified by our searches provided data on the effects of chronic AED use on the driving performance of individuals with epilepsy.

2. **The chronic use of AEDs for the treatment of epilepsy appears to have a deleterious impact on some (but not all) measures of cognitive and psychomotor function thought to be related to driving ability (Strength of Evidence: Acceptable)**

   Two studies (Median Quality: Low) that enrolled a total of 182 individuals met the inclusion criteria for Key Question 6. One study was a non-randomized controlled trial which compared cognitive and psychomotor function in 16 adults with epilepsy who were on chronic AED therapy with 16 individuals without epilepsy (Study Quality: 5.0: Low). The second study (Study Quality:8.2: High) was a randomized controlled trial which compared the effect of discontinuation of chronic AED monotherapy on measures of attention, reaction time, and speed of information processing in with that observed among a group of individuals who remained on AED therapy.

   The results of the first study demonstrated no difference between individuals with epilepsy who were using AED therapy and individuals without epilepsy in the cognitive and psychomotor domains of selective attention, memory functioning, or executive functioning. Overall, the authors concluded that there were no objective impairments in the cognitive and psychomotor domains; however, a lower speed of information processing affecting everyday life functioning was detected. Engelberts et al. concluded that individuals with a) well-controlled epilepsy, b) age at onset >18 years old, and c) a long duration of epilepsy, d) who are seizure free (a group analogous to the population of interest for the purposes of the FMCSA) comprised a distinct subpopulation of individuals who did not demonstrate cognitive or psychomotor deficits associated with chronic AED use. The authors then compared these results with a previous study (which did not meet inclusion criteria and was not included in the evidence base for this key question) that demonstrated cognitive and psychomotor

deficits in individuals with a maximum of one seizure per month (not seizure free), without restrictions on age at onset or epilepsy duration. In addition, speed of information processing results found in this study accorded with the results found in the previous study mentioned by Engelberts.

The results of the second study demonstrated that the group of individuals who had been seizure free for >2 years and been randomized to discontinue AED use, experienced improved performance on cognitive and psychomotor tests that required complex cognitive processing under pressure, including divided attention, rapid language discrimination, and rapid form discrimination when compared with the performance of these tests in individuals who had been randomized to continue AED therapy. There was no difference detected between the group of individuals who had undergone AED withdrawal and the group of individuals who were randomized to continue AED therapy in tests of sequential reaction time or simple reaction time. Outcomes were similar when examining results of the cognitive and psychomotor tests between individuals grouped by drug type (carbamazepine [CBZ] or valproic acid [VPA]). The authors suggest that individuals with epilepsy who are seizure-free may experience improved cognitive performance with AED discontinuation.

Overall, the results of the included studies would indicate that there are cognitive and psychomotor deficits associated with chronic AED use. Because several differences exist between the included studies, such as: inclusion of healthy volunteers as a control group, differences in drugs included in the studies, and differences in the cognitive and psychomotor tests used, a direct comparison between the results of the studies could not be made. Ultimately, the small size of the evidence base and its low quality precludes one from drawing an evidence-based conclusion on effects of AED use on driving simulator related cognitive and psychomotor function.

APPENDIX C: Evidence on Seizure Occurrence and Recurrence Rates among Individuals who have Experienced ≥ One Unprovoked Seizure

Crash Risk

- Tiller M, Tregear SJ, Price N, et al. Seizure Disorders and Commercial Motor Vehicle Driver Safety – Evidence Report. Prepared by Manila Consulting Incorporated and the ECRI Institute for FMCSA (In Press).

Recurrence Risk among Individuals with Epilepsy seizure free on Pharmacotherapy

- Tiller M, Tregear SJ, Price N, et al. Seizure Disorders and Commercial Motor Vehicle Driver Safety – Evidence Report. Prepared by Manila Consulting Incorporated and the ECRI Institute for FMCSA (In Press).

Seizure Recurrence Risk among Individuals with Epilepsy seizure free after Surgery

- Tiller M, Tregear SJ, Price N, et al. Seizure Disorders and Commercial Motor Vehicle Driver Safety – Evidence Report. Prepared by Manila Consulting Incorporated and the ECRI Institute for FMCSA (In Press).

Seizure Recurrence Risk following Single Unprovoked Seizure

- Tiller M, Tregear SJ, Price N, et al. Seizure Disorders and Commercial Motor Vehicle Driver Safety – Evidence Report. Prepared by Manila Consulting Incorporated and the ECRI Institute for FMCSA (In Press).

APPENDIX D: Evidence on Seizure Occurrence and Recurrence Rates Following an Exposure to a Potentially Provocative Factor

This appendix contains citations and abstracts for articles identified by a series of supplemental searches performed following the MEP meeting. The citations pertain to the risks of seizure occurrence (immediate, early, or late) and recurrence following exposure to a potential seizure provoking factor. Studies described by articles that are not in the English language that enrolled only children, or that were reports of interesting cases are not included among the citations listed here.

Head Trauma

- Agrawal, A., J. Timothy, et al. (2006). "Post-traumatic epilepsy: an overview." Clin Neurol Neurosurg 108(5): 433-9.
- Annegers, J. F. and S. P. Coan (2000). "The risks of epilepsy after traumatic brain injury." Seizure 9(7): 453-7.
- Annegers, J. F., J. D. Grabow, et al. (1980). "Seizures after head trauma: a population study." Neurology 30(7 Pt 1): 683-9.
- Annegers, J. F., W. A. Hauser, et al. (1998). "A population-based study of seizures after traumatic brain injuries." N Engl J Med 338(1): 20-4.
- Annegers, J. F., W. A. Hauser, et al. (1995). "Incidence of acute symptomatic seizures in Rochester, Minnesota, 1935-1984." Epilepsia 36(4): 327-33.
- Asikainen, I., M. Kaste, et al. (1999). "Early and late posttraumatic seizures in traumatic brain injury rehabilitation patients: brain injury factors causing late seizures and influence of seizures on long-term outcome." Epilepsia 40(5): 584-9.
- Caveness, W. F. (1976). "Epilepsy, a product of trauma in our time." Epilepsia 17(2): 207-15.
- De Santis, A., E. Sganzerla, et al. (1992). "Risk factors for late posttraumatic epilepsy." Acta Neurochir Suppl (Wien) 55: 64-7.
- Desai, B. T., S. Whitman, et al. (1983). "Seizures and civilian head injuries." Epilepsia 24(3): 289-96.
- Deymeer, F. and A. Leviton (1985). "Posttraumatic seizures: an assessment of the epidemiologic literature." Cent Nerv Syst Trauma 2(1): 33-43.
- Frey, L. C. (2003). "Epidemiology of posttraumatic epilepsy: a critical review." Epilepsia 44 Suppl 10: 11-7.
- Haltiner, A. M., N. R. Temkin, et al. (1997). "Risk of seizure recurrence after the first late posttraumatic seizure." Arch Phys Med Rehabil 78(8): 835-40.
- Lee, S. T., T. N. Lui, et al. (1995). "Early seizures after moderate closed head injury." Acta Neurochir (Wien) 137(3-4): 151-4.
- Lee, S. T., T. N. Lui, et al. (1997). "Early seizures after severe closed head injury." Can J Neurol Sci 24(1): 40-3.
- Pohlmann-Eden, B. and J. Bruckmeir (1997). "Predictors and dynamics of posttraumatic epilepsy." Acta Neurol Scand 95(5): 257-62.

- Sabhesan, S. and M. Natarajan (1993). "Long-term outcome following head injury." J Indian Med Assoc 91(2): 37-9.
- Salazar, A. M., B. Jabbari, et al. (1985). "Epilepsy after penetrating head injury. I. Clinical correlates: a report of the Vietnam Head Injury Study." Neurology 35(10): 1406-14.
- Segatore, M. and M. Jacobs (1993). "Posttraumatic seizures: consensus and controversies." Axone 15(2): 34-9.
- Singer, R. B. (2001). "Incidence of seizures after traumatic brain injury--a 50-year population survey." J Insur Med 33(1): 42-5.
- Weiss, G. H. and W. F. Caveness (1972). "Prognostic factors in the persistence of posttraumatic epilepsy." J Neurosurg 37(2): 164-9.
- Yablon, S. A. (1993). "Posttraumatic seizures." Arch Phys Med Rehabil 74(9): 983-1001.
- Yoshii, N., H. Samejima, et al. (1978). "Posttraumatic epilepsy and CT scan." Neuroradiology 16: 311-3.

Cerebrovascular Abnormalities, Intracerebral Hemorrhage, and Stroke

- Arboix, A., L. Garcia-Eroles, et al. (1997). "Predictive factors of early seizures after acute cerebrovascular disease." Stroke 28(8): 1590-4.
- Asconape, J. J. and J. K. Penry (1991). "Poststroke seizures in the elderly." Clin Geriatr Med 7(3): 483-92.
- Berger, A. R., R. B. Lipton, et al. (1988). "Early seizures following intracerebral hemorrhage: implications for therapy." Neurology 38(9): 1363-5.
- Bidzinski, J., A. Marchel, et al. (1992). "Risk of epilepsy after aneurysm operations." Acta Neurochir (Wien) 119(1-4): 49-52.
- Bladin, C. F., A. V. Alexandrov, et al. (2000). "Seizures after stroke: a prospective multicenter study." Arch Neurol 57(11): 1617-22.
- Buczacki, S. J., P. J. Kirkpatrick, et al. (2004). "Late epilepsy following open surgery for aneurysmal subarachnoid haemorrhage." J Neurol Neurosurg Psychiatry 75(11): 1620-2.
- Burn, J., M. Dennis, et al. (1997). "Epileptic seizures after a first stroke: the Oxfordshire Community Stroke Project." Bmj 315(7122): 1582-7.
- Butzkueven, H., A. H. Evans, et al. (2000). "Onset seizures independently predict poor outcome after subarachnoid hemorrhage." Neurology 55(9): 1315-20.
- Byrne, J. V., P. Boardman, et al. (2003). "Seizures after aneurysmal subarachnoid hemorrhage treated with coil embolization." Neurosurgery 52(3): 545-52; discussion 550-2.
- Cheung, C. M., T. H. Tsoi, et al. (2003). "Epileptic seizure after stroke in Chinese patients." J Neurol 250(7): 839-43.
- Claassen, J., S. Peery, et al. (2003). "Predictors and clinical impact of epilepsy after subarachnoid hemorrhage." Neurology 60(2): 208-14.
- Faught, E., D. Peters, et al. (1989). "Seizures after primary intracerebral hemorrhage." Neurology 39(8): 1089-93.
- Feleppa, M., W. Di Iorio, et al. (2006). "Early poststroke seizures." Clin Exp Hypertens 28(3-4): 265-70.

- Giroud, M., P. Gras, et al. (1994). "Early seizures after acute stroke: a study of 1,640 cases." Epilepsia 35(5): 959-64.
- Gupta, S. R., M. H. Naheedy, et al. (1988). "Postinfarction seizures. A clinical study." Stroke 19(12): 1477-81.
- Hart, R. G., J. A. Byer, et al. (1981). "Occurrence and implications of seizures in subarachnoid hemorrhage due to ruptured intracranial aneurysms." Neurosurgery 8(4): 417-21.
- Huff, J. S. and A. D. Perron (2001). "Onset seizures independently predict poor outcome after subarachnoid hemorrhage." Neurology 56(10): 1423-4.
- Kilpatrick, C. J., S. M. Davis, et al. (1990). "Epileptic seizures in acute stroke." Arch Neurol 47(2): 157-60.
- Labovitz, D. L., W. A. Hauser, et al. (2001). "Prevalence and predictors of early seizure and status epilepticus after first stroke." Neurology 57(2): 200-6.
- Lancman, M. E., A. Golimstok, et al. (1993). "Risk factors for developing seizures after a stroke." Epilepsia 34(1): 141-3.
- Lin, C. L., A. S. Dumont, et al. (2003). "Characterization of perioperative seizures and epilepsy following aneurysmal subarachnoid hemorrhage." J Neurosurg 99(6): 978-85.
- Lo, Y. K., C. H. Yiu, et al. (1994). "Frequency and characteristics of early seizures in Chinese acute stroke." Acta Neurol Scand 90(2): 83-5.
- Ogden, J. A., T. Utley, et al. (1997). "Neurological and psychosocial outcome 4 to 7 years after subarachnoid hemorrhage." Neurosurgery 41(1): 25-34.
- Ohman, J. (1990). "Hypertension as a risk factor for epilepsy after aneurysmal subarachnoid hemorrhage and surgery." Neurosurgery 27(4): 578-81.
- Olafsson, E., G. Gudmundsson, et al. (2000). "Risk of epilepsy in long-term survivors of surgery for aneurysmal subarachnoid hemorrhage: a population-based study in Iceland." Epilepsia 41(9): 1201-5.
- O'Laoire, S. A. (1990). "Epilepsy following neurosurgical intervention." Acta Neurochir Suppl (Wien) 50: 52-4.
- Passero, S., R. Rocchi, et al. (2002). "Seizures after spontaneous supratentorial intracerebral hemorrhage." Epilepsia 43(10): 1175-80.
- Pinto, A. N., P. Canhao, et al. (1996). "Seizures at the onset of subarachnoid haemorrhage." J Neurol 243(2): 161-4.
- Rhoney, D. H., L. B. Tipps, et al. (2000). "Anticonvulsant prophylaxis and timing of seizures after aneurysmal subarachnoid hemorrhage." Neurology 55(2): 258-65.
- Sitajayalakshmi, S., J. Mani, et al. (2002). "Post stroke epilepsy." Neurol India 50 Suppl: S78-84.
- Sundaram, M. B. and F. Chow (1986). "Seizures associated with spontaneous subarachnoid hemorrhage." Can J Neurol Sci 13(3): 229-31.
- Sung, C. Y. and N. S. Chu (1989). "Epileptic seizures in intracerebral haemorrhage." J Neurol Neurosurg Psychiatry 52(11): 1273-6.
- Vespa, P. M., K. O'Phelan, et al. (2003). "Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome." Neurology 60(9): 1441-6.
- Weisberg, L. A., M. Shamsnia, et al. (1991). "Seizures caused by nontraumatic parenchymal brain hemorrhages." Neurology 41(8): 1197-9.

Neurocysticercosis

- Carpio, A. and W. A. Hauser (2002). "Prognosis for seizure recurrence in patients with newly diagnosed neurocysticercosis." Neurology 59(11): 1730-4.
- Dansey, R. D., M. Hay, et al. (1992). "Seizures and neurocysticercosis in black men." S Afr Med J 81(8): 424-5.
- Del Brutto, O. H. (1994). "Prognostic factors for seizure recurrence after withdrawal of antiepileptic drugs in patients with neurocysticercosis." Neurology 44(9): 1706-9.
- Del Brutto, O. H., R. Santibanez, et al. (1992). "Epilepsy due to neurocysticercosis: analysis of 203 patients." Neurology 42(2): 389-92.
- Garcia, H. H., E. J. Pretell, et al. (2004). "A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis." N Engl J Med 350(3): 249-58.
- Kumar Garg, R. (2003). "Risk of seizure recurrence in patients with neurocysticercosis." Natl Med J India 16(2): 90-1.
- Leite, J. P., V. C. Terra-Bustamante, et al. (2000). "Calcified neurocysticercotic lesions and postsurgery seizure control in temporal lobe epilepsy." Neurology 55(10): 1485-91.
- Medina, M. T., P. Genton, et al. (1993). "Effect of anticysticercal treatment on the prognosis of epilepsy in neurocysticercosis: a pilot trial." Epilepsia 34(6): 1024-7.
- Montano, S. M., M. V. Villaran, et al. (2005). "Neurocysticercosis: association between seizures, serology, and brain CT in rural Peru." Neurology 65(2): 229-33.
- Monteiro, L., T. Coelho, et al. (1992). "Neurocysticercosis--a review of 231 cases." Infection 20(2): 61-5.
- Monteiro, L., B. Nunes, et al. (1995). "Spectrum of epilepsy in neurocysticercosis: a long-term follow-up of 143 patients." Acta Neurol Scand 92(1): 33-40.
- Murthy, J. (2006). "Seizures associated with solitary cysticercus granuloma: antiepileptic drugs for how long?" Neurol India 54(2): 141-2.
- Nash, T. E. (2003). "Human case management and treatment of cysticercosis." Acta Trop 87(1): 61-9.
- Nash, T. E., J. Pretell, et al. (2001). "Calcified cysticerci provoke perilesional edema and seizures." Clin Infect Dis 33(10): 1649-53.
- Ong, S., D. A. Talan, et al. (2002). "Neurocysticercosis in radiographically imaged seizure patients in U.S. emergency departments." Emerg Infect Dis 8(6): 608-13.
- Rajshekhar, V. and L. Jeyaseelan (2004). "Seizure outcome in patients with a solitary cerebral cysticercus granuloma." Neurology 62(12): 2236-40.
- Sanchetee, P. C., C. S. Venkataraman, et al. (1991). "Epilepsy as a manifestation of neurocysticercosis." J Assoc Physicians India 39(4): 325-8.
- Santos, I. C., E. Kobayashi, et al. (2000). "Cysticidal therapy: impact on seizure control in epilepsy associated with neurocysticercosis." Arq Neuropsiquiatr 58(4): 1014-20.
- Vazquez, V. and J. Sotelo (1992). "The course of seizures after treatment for cerebral cysticercosis." N Engl J Med 327(10): 696-701.

- Velasco, T. R., P. A. Zanello, et al. (2006). "Calcified cysticercotic lesions and intractable epilepsy: a cross sectional study of 512 patients." J Neurol Neurosurg Psychiatry 77(4): 485-8.
- Verma, A. and S. Misra (2006). "Outcome of short-term antiepileptic treatment in patients with solitary cerebral cysticercus granuloma." Acta Neurol Scand 113(3): 174-7.

Viral Encephalitis

- Annegers, J. F., W. A. Hauser, et al. (1988). "The risk of unprovoked seizures after encephalitis and meningitis." Neurology 38(9): 1407-10.

Meningitis

- Annegers, J. F., W. A. Hauser, et al. (1988). "The risk of unprovoked seizures after encephalitis and meningitis." Neurology 38(9): 1407-10.
- Rosman, N. P., D. B. Peterson, et al. (1985). "Seizures in bacterial meningitis: prevalence, patterns, pathogenesis, and prognosis." Pediatr Neurol 1(5): 278-85.
- Wang, K. W., W. N. Chang, et al. (2005). "The significance of seizures and other predictive factors during the acute illness for the long-term outcome after bacterial meningitis." Seizure 14(8): 586-92.

General

- Annegers, J. F., W. A. Hauser, et al. (1995). "Incidence of acute symptomatic seizures in Rochester, Minnesota, 1935-1984." Epilepsia 36(4): 327-33.
- Bernal, B. and N. R. Altman (2003). "Evidence-based medicine: neuroimaging of seizures." Neuroimaging Clin N Am 13(2): 211-24.
- Bonilha, L., F. Cendes, et al. (2004). "Epilepsy due to a destructive brain lesion caused by a scorpion sting." Arch Neurol 61(8): 1294-6.[3]
- Bromfield, E. B. (2004). "Epilepsy in patients with brain tumors and other cancers." Rev Neurol Dis 1 Suppl 1: S27-33.
- Ferro, J. M., M. Correia, et al. (2003). "Seizures in cerebral vein and dural sinus thrombosis." Cerebrovasc Dis 15(1-2): 78-83.
- Gelisse, P., J. C. Samuelian, et al. (1999). "Is schizophrenia a risk factor for epilepsy or acute symptomatic seizures?" Epilepsia 40(11): 1566-71.
- Guerrini, R. and P. Genton (2004). "Epileptic syndromes and visually induced seizures." Epilepsia 45 Suppl 1: 14-8.
- Hauser, W. A. (1992). "Seizure disorders: the changes with age." Epilepsia 33 Suppl 4: S6-14.
- Hesdorffer, D. C. and M. D'Amelio (2005). "Mortality in the first 30 days following incident acute symptomatic seizures." Epilepsia 46 Suppl 11: 43-5.
- Hesdorffer, D. C., G. Logroscino, et al. (1998). "Risk of unprovoked seizure after acute symptomatic seizure: effect of status epilepticus." Ann Neurol 44(6): 908-12.

[3] While this is a case report it is included because it provides a nice example of where a single exposure to a toxin can result in a brain lesion and recurrent seizures.

- Holstege, C. P. and A. B. Baer (2004). "Insecticides." Curr Treat Options Neurol 6(1): 17-23.
- Holstege, C. P. and S. G. Dobmeier (2005). "Nerve Agent Toxicity and Treatment." Curr Treat Options Neurol 7(2): 91-98.
- Kao, L. W. and K. A. Nanagas (2004). "Carbon monoxide poisoning." Emerg Med Clin North Am 22(4): 985-1018.
- Koppel, B. S., L. Samkoff, et al. (1996). "Relation of cocaine use to seizures and epilepsy." Epilepsia 37(9): 875-8.
- Murthy, J. M. and R. Yangala (1999). "Acute symptomatic seizures - incidence and etiological spectrum: a hospital-based study from South India." Seizure 8(3): 162-5.
- Narayanan, J. T. and J. Murthy (2007). "New-onset acute symptomatic seizure in a neurological intensive care unit." Neurol India 55(2): 136-40.
- Parmar, H., S. H. Lim, et al. (2006). "Acute symptomatic seizures and hippocampus damage: DWI and MRS findings." Neurology 66(11): 1732-5.
- Thussu, A., A. Arora, et al. (2002). "Acute symptomatic seizures due to single CT lesions: how long to treat with antiepileptic drugs?" Neurol India 50(2): 141-4.