Evidence Report:
Seizure Disorders and Commercial Motor Vehicle Driver Safety (Comprehensive Review)

Presented to

Federal Motor Carrier Safety Administration

November 30, 2007

Prepared for

MANILA Consulting Group, Inc.

MANILA Consulting Group, Inc.
1420 Beverly Road, Suite 220
McLean, VA 22101

Prepared by

ECRI
A NONPROFIT AGENCY

ECRI
5200 Butler Pike
Plymouth Meeting, PA 19462

This report is comprised of research conducted to analyze the impact of Seizure Disorders on Commercial Motor Vehicle Driver Safety. Federal Motor Carrier Safety Administration considers evidence, expert recommendations, and other data, however, all proposed changes to current standards and guidance (guidelines) will be subject to public-notice-and-comment and regulatory processes.

Policy Statement

This evidence report was prepared by ECRI under subcontract to MANILA Consulting Group, Inc., which holds prime Contract No: GS-10F-0177N/DTMC75-06-F-00039 with the Department of Transportation's Federal Motor Carrier Safety Administration. ECRI is an independent, nonprofit health services research agency and a Collaborating Center for Health Technology Assessment of the World Health Organization. ECRI has been designated an Evidence-based Practice Center (EPC) by the United States Agency for Healthcare Research and Quality. ECRI's mission is to provide information and technical assistance to the healthcare community worldwide to support safe and cost-effective patient care. The results of ECRI's research and experience are available through its publications, information systems, databases, technical assistance programs, laboratory services, seminars, and fellowships. The purpose of this evidence report is to provide information regarding the current state of knowledge on this topic. It is not intended as instruction for medical practice, or for making decisions regarding individual patients.

Table of Contents

Table of Contents

Tables

Figures

Executive Summary

Purpose of Evidence Report

Of all occupations in the United States, workers in the trucking industry experience the third highest fatality rate, accounting for 12 percent of all worker deaths. About two-thirds of fatally injured truck workers were involved in highway crashes. According to statistics from the United States Department of Transportation (DOT), there were 4,932 fatal crashes involving a large truck in 2005 for a total of 5,212 fatalities. In addition, there were 137,144 non-fatal crashes; 59,405 of these were crashes that resulted in an injury to at least one individual (for a total of 89,681 injuries).

The purpose of this evidence report is to address several key questions posed by Federal Motor Carrier Safety Administration (FMCSA). FMCSA developed ach 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 this evidence report are:

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 anti-epilepsy drug (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[1] 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 this 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,

[1] >2 weeks treatment

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.*

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 made a clear distinction between qualitative and quantitative conclusions and we assigned a separate strength-of-evidence rating to each of conclusion format. The strength-of-evidence ratings assigned to these different types of conclusion is defined in Table 1.

Table 1. 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 this 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 sufficient 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 reoccur 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 12 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 (see Background section) 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. Also, the reader should note that our findings do not pertain to all individuals who have undergone surgery for epilepsy. Rather, they 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 can be drawn.

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 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.

Preface

Organization of Report

This evidence report contains five major sections: 1) *Background*, 2) *Current U.S. Federal Regulatory and Medical Advisory Criteria*, 3) *Methods*, 4) *Synthesis of Results*, and 5) *Conclusions*. These major sections are supplemented by extensive use of appendices.

In the *Background* section, we provide background information about epilepsy, including details about its epidemiology, diagnosis, treatment, and potential impact on driver safety. In the *Current United States Regulatory and Medical Advisory Criteria* section we provide information about epilepsy and seizure-related standards and guidelines for commercial motor vehicle (CMV) operators in the U.S. and several other countries. In addition we provide pertinent information as it pertains to commercial pilots, merchant mariners, and railcar operators. In the *Methods* section, we detail how we identified and analyzed information for this report. The section covers the key questions addressed, details of literature searches, criteria for including studies in our analyses, evaluation of study quality, assessment of the strength of the evidence base for each question, and methods for abstracting and synthesizing clinical study results. The *Synthesis of Results* section of this report is organized by Key Question. For each question, we report on the quality and quantity of the studies that provided relevant evidence. We then summarize available data extracted from included studies either qualitatively or, when data permit, qualitatively and quantitatively (using meta-analysis). Each section in the Synthesis of Results section closes with conclusions based on our assessment of the available evidence. The evidence report ends with a *Conclusions* section that briefly summarizes the answers to each of the questions addressed in it.

Scope of Report

Commercial driving is a hazardous occupation. The trucking industry has the third highest fatality rate (12 percent of all occupation-related deaths) in the U.S. About two-thirds of fatally injured truck workers were involved in highway crashes. According to the U.S. Department of Transportation (DOT), there were 137,144 non-fatal crashes involving a large truck in 2005. In addition, 59,405 of those crashes resulted in an injury to at least one individual, for a total of 89,681 injuries; and 4,932 of all crashes caused 5,215 fatalities.

The purpose of this evidence report is to address several key questions posed by the FMCSA. FMCSA carefully formulated each of these key questions so that its answer will provide information necessary for updating its report, "Conference on Neurological Disorders and Commercial Drivers." The Key Questions addressed in this evidence report are as follows:

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 a 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.

[2] >2 weeks treatment

Background

Commercial driving is a hazardous occupation. The trucking industry has the third highest fatality rate (12 percent of all occupation-related deaths) in the U.S. (http://www.bls.gov/iif/oshcfoiarchive.htm#2004charts). About two-thirds of fatally injured truck workers were involved in highway crashes. According to the DOT, there were 137,144 non-fatal crashes involving a large truck in 2005. In addition, 59,405 of those crashes resulted in an injury to at least one individual, for a total of 89,681 injuries; and 4,932 of all crashes caused 5,215 fatalities (http://ai.volpe.dot.gov/CrashProfile/CrashProfileMainNew.asp?dy=2005).

Seizure disorders may culminate in unpredictable and sudden incapacitation, thus contributing to the potential for crash, injury, and death. The purpose of this evidence report is to assess and summarize the available data on the relationship between seizure disorders and motor vehicle crash risk.

Epilepsy

Epilepsy is a central nervous system disorder characterized by recurrent involuntary seizures resulting from excessive hypersynchronous discharges of neurons in the brain. Epilepsy is not a distinct disease; rather, it is a group of disorders for which recurrent seizures are the main symptom. Seizures begin with "two concurrent events: 1) high-frequency bursts of action potentials, and 2) hypersynchronization of a neuronal population"(15,16), which then propagate in the brain when there is enough electrical activity to recruit neurons surrounding the point of origin. When propagation occurs, surround inhibition is lost and seizure activity spreads through local connections and long association pathways to other parts of the brain.

Seizures can be 'subclinical' (only detected on an electroencephalogram) or cause objective clinical signs and subjective symptoms, such as loss of consciousness, tonic/clonic muscle contractions, sensory phenomena (visual or olfactory hallucinations), or abnormal behaviors that interfere with normal functioning. Seizures are not a disease, but serve as an indicator of underlying pathology such as central nervous system infection, cerebral hypoxia, hyperglycemia, alcohol or drug withdrawal, brain tumor, or cerebrovascular disease. Depending on the source of the seizures, epileptic seizures are categorized as either asymptomatic epilepsy, in which the cause of the epilepsy does not appear to be related to a recognized insult or condition, or symptomatic epilepsy, which usually arises from a particular cause which may be eliminated with therapeutic intervention.

Seizures

A seizure is generally defined as a rapid, temporary alteration of electrical activity in the brain (usually in the cortex) which results in changes to an individual's behavior. They have a beginning, which may or may not be noticed by the individual as an 'aura' or 'warning' state (Table 2); a middle, which may simply remain as an aura or may progress to a complex partial seizure (see the section subheading Seizures for further information on seizure classifications and definitions) or convulsions (Table 3); and an end, known as the post-ictal phase, which signifies the transition from seizure to the individuals normal state (Table 4). Seizure disorders can be

divided into two categories: the isolated, non-recurrent seizure event and seizures resulting from cortical/cerebral dysfunction that are recurrent (commonly known as epilepsy).

Table 2. Early Warning Signs of Seizure

Psychic	Emotional	Physical	No Warning
Déjà vu	Fear / Panic	Dizziness	Seizure may arrive without warning
Jamais vu	Pleasant feeling	Headache	
Smell		Lightheadedness	
Sound		Nausea	
Taste		Numbness	
Vision blurring or loss			
Racing thoughts			
Stomach symptoms			
General feeling of 'not being right'			
Tingling			

Table 3. Symptoms of a Seizure

Psychic	Emotional	Physical
Black out	Fear / Panic	Chewing movements
Confusion		Convulsion
Deafness/Sounds		Difficulty talking
"Electric Shock" feeling		Drooling
Loss of consciousness		Eyelid fluttering
Smell		Eyes rolled up
"Spacing out"		Falling down
"Out of body" experience		Foot stomping
Visual loss or blurring		Hand waving
		Inability to move
		Incontinence
		Lip smacking
		Making noises
		Shaking
		Staring
		Stiffening
		Swallowing
		Sweating
		Teeth clenching/grinding
		Tongue biting
		Tremors
		Twitching movements
		Breathing difficulty
		Heart racing

Table 4. Post-ictal symptoms of Seizure

Psychic	Emotional	Physical
Memory loss	Confusion	Bruising
Writing difficulty	Depression and Sadness	Difficulty speaking
	Fear	Injuries
	Frustration	Sleeping
	Shame / Embarrassment	Exhaustion
		Headache
		Nausea
		Pain
		Thirst
		Weakness
		Urge to urinate / defecate

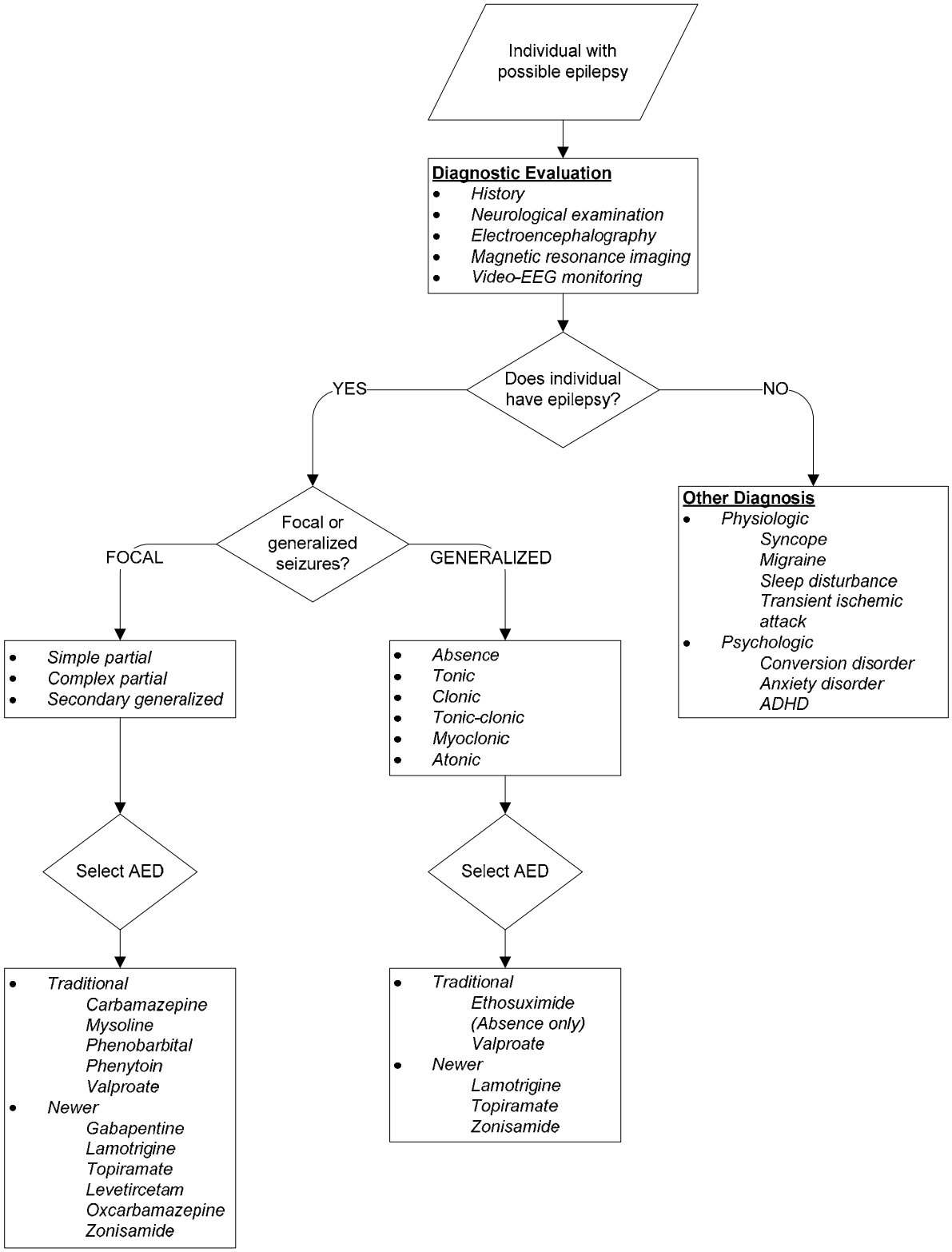
Acute Provoked Seizures

Some seizures occur as a response to a provocative factor such as fever, head trauma, ischemic stroke, and space occupying lesions such as dysembryoplastic neuroepithelial tumors (DNETS). Such seizures are defined as 'acute symptomatic' seizures, 'secondary' seizures, or 'situation-related' seizures. These seizures are considered an acute response to an abnormal situation which has altered or impaired brain function.(17) Most acute symptomatic or secondary seizures are unlikely to recur: however, it is estimated that between 3 and 10 percent of all individuals who experience this kind of seizure will have experience seizure recurrence.(18) Even if recurrent, these seizures are not classified as epilepsy.(19) Population-based studies of seizures indicate that 25-30 percent of first seizures are acute/symptomatic, or provoked by factors such as the examples previously listed.(18) Seizures related to specific 'triggers' (reflex epilepsies) such as stroboscopic light patterns or somatosensory stimuli are associated in susceptible individuals with an underlying epilepsy disorder, and are not considered acute or symptomatic.

Differentiating Epileptic from Non-Epileptic Seizures

The differentiation of epileptic from non-epileptic seizures is vital in determining whether treatment is required, what the proper course of treatment should constitute, and potential consequences involving changes in behavior and lifestyle. LaRoche and Helmers(20) (http://jama.ama-assn.org/cgi/content/full/291/5/605) created an algorithm to aid in the diagnosis and treatment of recurrent seizures (Figure 1).

Figure 1. LaRoche and Helmer Algorithm for Diagnosis and Treatment of Recurrent Seizures



The Classification of Epileptic Seizures

Understanding the type of seizure an individual experiences is critical in helping to determine the best treatment of the options currently available. According to the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE)(21) (also available online at http://neuroland.com), seizures are classified as partial (a localized neural discharge that involves only one region of the cerebral cortex) or generalized (a bilateral neural discharge which diffuses to involve the entire cerebral cortex). This classification system is presented in Table 5.

Table 5. ILAE Classification System for Seizures

I. Partial (focal, local) seizure
a. Simple partial seizures (SPS): involves only part of the brain and does not impair consciousness
i. Motor, somatosensory, autonomic, or psychic symptoms
b. Complex, partial seizures (CPS)
i. Begin with symptoms of SPS but progress to impairment of consciousness.
ii. Begin with impairment of consciousness
c. Partial seizures with secondary generalization
i. Begin with SPS.
ii. Begin with CPS (including those with symptoms of SPS at onset).
II. Generalized seizures (convulsive or non-convulsive): involves both sides of the brain, with tonic and clonic movements or absence or atonic characteristics
a. Absence (typical and atypical): formerly labeled 'petit mal', characterized by brief (± 20 seconds) staring that may be associated with blinking or brief automatic movements of the mouth or hands
b. Myoclonic: brief muscle jerk. May be normal / benign (as with muscle jerks that occur when falling asleep) or may result from an abnormal discharge of electrical activity in the brain
c. Clonic: jerking movements involving muscles on both sides of the body
d. Tonic: stiffening of muscles on both sides of the body, with electrical discharges involving most or all of the brain
e. Tonic-clonic (GTCSs) (with convulsions, formerly known as grand mal seizures)
f. Atonic / akinetic: seizure characterized by loss of muscle tone
III. Unclassified seizures

Partial seizures are divided into three categories: simple partial seizures, complex partial seizures, and partial seizures with secondary generalization. In simple partial seizures, the individual is alert, conscious, and can remember events that took place during the seizure. In complex partial seizures, however, the individual's consciousness is either impaired or lost, and the effected individual demonstrates a concomitant inability to recall events that took place during the seizure. In partial seizures with secondary generalization, an individual experiences a seizure that begins as a partial seizure and then progresses to a generalized event.

Generalized seizures are categorized into absence (formerly known as petit mal), atypical absence, myoclonic, atonic, tonic, and tonic-clonic types. Occurring without warning, typical absence seizures are generally brief (3-20 seconds) periods of staring with impaired cognition and awareness, with no deficit in awareness (no post-ictal period) after the seizure. Atypical absence seizures begin and end gradually, usually last between 5 and 30 seconds, and are accompanied by staring, with occasional eye blinking and lip twitching. Myoclonic seizures involve a 'brief, shock-like jerk of a muscle or group of muscles."(22) Everyone has experienced benign myoclonus, which is the brief jolting of muscles that occurs while falling asleep (also

known as hypnic jerk). Epileptic myoclonus causes a brief (< 1 second) synchronous jerking of the muscles of the neck, shoulders, upper arms, trunk, and upper legs, during which consciousness remains unimpaired. Atonic seizures are brief events (5 seconds to 1 minute) indicted by a 'sudden loss of posture tone,' which may be indicted by head nods, jaw drops, or falls, with impaired consciousness. These 'epileptic drop attacks' can also happen if the legs are affected by a myoclonic seizure. Tonic seizures are brief (5 to 20 seconds), usually nocturnal, generalized events involving the flexion and extension of symmetrical muscle groups in the trunk and neck, upper body, or lower body. Tonic-clonic seizures (grand mal or convulsive seizures) begin with a tonic phase followed by a clonic phase featuring muscle jerking of the arms and legs accompanied by loss of consciousness and, possibly, drooling, loss of bladder or bowel control, and biting of the cheek, tongue, or lips. Tonic-clonic seizures may last anywhere from 30 to 120 seconds, with the individual exhibiting lethargy and cognitive impairment during the post-ictal period.(22)

Jenssen et al.(23) systematically compared length of time for seizures in individuals with intractable epilepsy and found that seizure duration differed depending on the type of seizure experienced (Table 6). In this study, partial onset seizures that spread to both hemispheres in the brain had the longest duration, with simple generalized tonic-clonic seizures (SGTCS) unlikely to last more than 660 seconds (11 minutes), complex partial seizures (CPS) unlikely to last more than 600 seconds (10 minutes), and simple partial seizures (SPS) unlikely to last longer than 240 seconds (4 minutes). SGTCS, CPS, and SPS that lasted longer than the times quoted were likely to evolve into status epilepticus.

Table 6. Seizure Duration Statistics by Type of Seizure

Seizure Type	N	Median duration per patient in seconds	Longest duration per patient in seconds	Range of durations within patient in seconds	No. of seizures recorded
Tonic Seizure	7	18.5 (8-410)	34 (11-620)	21.25	57
Simple Partial Seizure	25	28 (3-180)	35 (3-475)	23.00	65
Partial Generalized Tonic-Clonic Seizure	6	66 (59-75)	68 (59-76)	2.50	8
Complex Partial Seizure	85	78 (8-298)	11 (40-960)	46.00	375
Simple Generalized Tonic-Clonic Seizure	34	130 (37-139)	142 (50-630	37.00	70

Adapted from data presented by Jenssen et al.(23)

The reader should note that some individuals with epilepsy cannot be easily classified into one of the categories defined by the ILAE seizure categorization system. This is because they may experience both partial seizures and generalized seizures in separate seizure events with no clear pattern apparent.(22) Such individuals would be classified under the ILAE system as having "unclassified seizures."

Epilepsy and Epileptic Syndromes

If a seizure arises as the sole manifestation of a neurologic disorder, it is termed *epilepsy*. If the seizure is part of a group of symptoms, however, it is considered to be *epileptic syndrome*, with

consideration accorded to age at onset, etiology, prognosis, and response to treatment.(18) Epileptic syndromes include: benign familial neonatal seizures, Ohtahara syndrome, startle epilepsy, and early onset benign childhood occipital epilepsy. The American Epilepsy Society's Annotated Proposal International Classification of Epilepsies and Epileptic Syndromes(21) are featured below.

1. **Localization-Related (Local, Focal, Partial) Epilepsies and Syndromes**
    a. **Idiopathic** (with age-related onset): disorder is not associated with other neurologic or neuropsychologic abnormalities
        i. Benign childhood epilepsy with centrotemporal spikes ('rolandic epilepsy')
        ii. Childhood epilepsy with occipital paroxysms
    b. Symptomatic: abnormality is present and cause is known
        i. Chronic progressive epilepsia partialis continua of childhood (e.g. 'Rasmussen's encephalitis')
        ii. Frontal lobe epilepsies
        iii. Occipital lobe epilepsies
        iv. Parietal lobe epilepsies
        v. Syndromes characterized by specific modes of precipitation
        vi. Temporal lobe epilepsies
    c. Cryptogenic: presumed to be symptomatic but the cause in the specific patient is unknown
2. **Generalized Epilepsies and Syndromes**
    a. **Idiopathic** (with age-related onset): disorder is not associated with other neurologic or neuropsychologic abnormalities
        i. Benign neonatal familial convulsions
        ii. Benign neonatal convulsions
        iii. Benign myoclonic epilepsy in childhood
        iv. Childhood absence epilepsy (pyknolepsy)
        v. Juvenile absence epilepsy
        vi. Juvenile myoclonic epilepsy
    b. Cryptogenic or Symptomatic: presumed to be symptomatic but the cause in the specific patient is unknown
        i. West syndrome
        ii. Lennox-Gastaut syndrome

3. Epilepsies and Syndromes Undetermined Whether Focal or Generalized

The National Institute of Neurological Disorders and Stroke (NINDS, 2001) has identified the following epileptic syndromes:(24)

a. **Absence Epilepsy** – Individuals have repeated absence seizures that cause momentary lapses of consciousness. Some individuals with absence seizures have purposefulness movements during their seizures, such as a jerking arm or rapidly blinking eyes.

b. **Psychomotor Epilepsy** – an alternate term for recurrent partial seizures, especially seizures of the temporal lobe. The term psychomotor refers to the strange sensations, emotions, and behavior seen with these seizures.

c. **Temporal Lobe Epilepsy (TLE))** – is the most common epilepsy syndrome with partial seizures. These seizures are often associated with auras. TLE often begins in childhood.

d. **Frontal Lobe Epilepsy** – usually involves a cluster of short seizures with sudden onset and termination. There are many subtypes of frontal lobe seizures. The symptoms depend on where in the frontal lobe the seizures occur.

e. **Occipital Lobe Epilepsy** – usually begins with visual hallucinations, rapid eye blinking, or other eye-related symptoms. Otherwise it resembles temporal or frontal lobe epilepsy.

f. **Parietal Lobe Epilepsy** – symptoms closely resemble those of other types of epilepsy. This may reflect the fact that parietal lobe seizures tend to spread to other areas of the brain.

Reflex Epilepsy

Epileptic seizures are usually an unpredictable event because of the complexity of factors precipitating an epileptic event. In some cases, factors associated with the production or reduction of epileptic seizures are identifiable (i.e. sleep deprivation, administration of AEDs), and steps may be taken to avoid or aid the factor in order to decrease the possibility of inducing a seizure. In contrast, *reflex epilepsy* involves a predictable response (a seizure) from a known localization to a specific functional stimulus. Reflex epilepsy may be asymptomatic or result from a specific and identifiable cause such as head trauma. Stimuli/triggers associated with reflex epilepsy include:

Vision: stroboscopic light patterns (associated with generalized seizures, i.e. absence, myoclonic, with possible progression to generalized tonic-clonic; complex partial seizures; or other types of seizures.) A reduction in light sensitivity (scotosensitive), removal of visual fixation (fixation-off sensitivity), or the frequency of flicker on a screen (photosensitivity) may also elicit a reaction. The region or system associated with the trigger is generally observed to be the occipital cortex.

Pattern-sensitivity: high contrast circles, lines, and check patterns, particularly if any of these patterns are oscillating or moving, may trigger an epileptic seizure. The region or system associated with the trigger is generally observed to be the magnocellular system of the occipital cortex.

Somatosensory stimuli: light touch, tapping, or immersion in hot water, are all known triggers. The region or system associated with the trigger is generally observed to be the primary or secondary somatosensory cortex.

Auditory: less commonly encountered than visually-triggered seizures, auditory related seizures include simple sounds (startle epilepsy, associated with gross or subtle perirolandic lesions) and music (musicogenic seizures, generally localized, rather than generalized, and associated with the temporal limbic and non-limbic areas of the brain).

More unusual reflex seizures include primary reading epilepsy (induced by the act of reading and associated with the right, or left, or bilateral temporoparietal lobe), thinking (induced by mathematical calculations, the processing of spatial information, and decision-making and associated with the parietal lobe), and eating epilepsy (seizures are triggered by the sight or smell of food and associated with presylvian lesions). Other complex activities associated with reflex epilepsy include brushing the teeth and walking.(25)

Nocturnal Epilepsy

Seizures that occur primarily during sleep are generally categorized as nocturnal epilepsy, with certain types of seizures appearing to be more commonly associated with sleep. In general, nocturnal seizures are treated with the same therapeutic agents as other epilepsy syndromes.

Not a great deal is actually known about nocturnal epilepsy, particularly because it is rarely witnessed. In a recent review paper, Ryvlin et al. further highlighted the general lack of information about nocturnal epilepsy by detailing knowledge deficits in the understanding the neural networks involved with the syndrome; neuropsychological profiles of individuals with nocturnal epilepsy; and quality of life measures involving daytime sleepiness and subjective sleep quality.(26,27) Further complicating our understanding of nocturnal epilepsy is the intricate relationship that epilepsy appears to have with sleep, meaning that nocturnal epilepsy may be frequently confused with a variety of normal and abnormal sleep events including: hypnic jerks (benign myoclonus), sleep ‘drunkenness’ (a prolonged state of confusion after waking), sleep paralysis, restless leg syndrome, sleep terrors, rapid eye movement (REM) behavior disorder, and hypersomnolence associated with severe sleep apnea.(28)

In general, seizures associated with nocturnal epilepsy occur just after the individual has fallen asleep, or just before they awaken. Specifically, the seizures occur most often within the first 2 hours of sleep (early nocturnal seizures), in the two hours previous to usual waking time, or in the first two hours after waking (early morning seizures). Taking this timing of seizures into account, the finding that REM sleep appears to have an inhibitive effect on some types of nocturnal seizures is interesting, albeit little understood.(28)

Most patients who have seizures only during the specific times noted above have idiopathic epilepsy, Frontal lobe involvement (which is unlikely to generalize) is largely suspected due to the ictal signs present during the seizure event.(28) Temporal lobe involvement (which is more likely to secondarily generalize) has also been noted, leading to questions regarding different neural pathways in partial seizure distribution.

Currently nocturnal epilepsy syndromes include:

1. Nocturnal Frontal Lobe Epilepsy (NFLE): a disorder characterized by seizures that occur almost exclusively during sleep. It encompasses a variety of seizure types, drug resistance has been reported in approximately 30 percent of patients. A recent study by Vignatelli et al. concluded that NFLE was generally not associated with excessive daytime sleepiness as measured by the Epworth Sleepiness Scale, although daytime sleepiness symptoms in individuals with subjective disturbed sleep quality may be related to nocturnal seizure activity (without reference to the number of seizures experienced per sleep period).
2. Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE): a rare, usually familial seizure disorder associated with a gene mutation locus 20q13.2-q13.3, ADNFLE has been observed to occur during sleep in clusters associated with partial seizures with tonic extension, mouth movement, and unintelligible speech.
3. Awakening Tonic-Clonic seizures: these seizures tend to occur in the early morning hours after an individual awakes, with some individuals experiencing a second round of seizures in the early evening. Individuals with awakening tonic-clonic seizures may be particularly sensitive to sleep deprivation or alcohol consumption. Seizures associated with awakening tonic-clonic seizures usually respond well to pharmaceutical therapy.
4. Landau-Kleffner Syndrome (LKS): a condition of acquired aphasia that may also include epileptic seizures and an epileptiform electroencephalogram (EEG) during sleep. Seizures associated with LKS usually respond well to pharmaceutical therapy.

Pathophysiology of Epilepsy

As stated previously, epilepsy is a central nervous system disorder characterized by recurrent involuntary seizures resulting from excessive hypersynchronous discharges of neurons in the brain. The ictal seizure begins with a localized prolonged depolarization, including the rapid firing of repeated action potentials, in a small group of neurons. Adjacent and/or connected neurons are recruited, with a clinical seizure progressing from an ictal seizure when a large number of affected cells experiencing the electrical discharges become linked. At this point, the seizure may spread to other areas in the brain.(15)

Proposed mechanisms for the generation and propagation of seizure activity in the brain include: neuron membrane abnormalities which result in a disruption to the depolarization and repolarization of the mechanisms of the cell (i.e. excitability of neuronal tissue); irregular neural networks which develop aberrant synchronization of a group of cells (synchronization of neural tissue); decreases in gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission, and increases in glutamate-mediated excitatory neurotransmission. Genetic information, which controls a number of intracellular processes such as cell structure, receptor functions, and ionic channels, plays a part in the potential for seizure activity.(15,22) It should be noted that none of the available models of epileptogenesis in humans has been clinically validated.(29)

Structurally, the two areas of the brain most commonly associated with seizure activity are the cerebral neocortex and the hippocampus. Common causes of seizures in infants and children include congenital malformations, perinatal injuries and/or hypoxia, metabolic defects, injury, and infection. In young adults, seizures are most often linked to head trauma, tumors, and infection. In the elderly, seizures are commonly associated with cerebrovascular disease and brain tumors.

Risk Factors for Epilepsy

Risk factors which may be associated with the development of epilepsy include:

- Genetics: A family history of epilepsy
- Age: younger and older individuals have a higher incidence and prevalence rate of epilepsy, but generally have different types of epilepsy disorders and different etiologies.
- Brain injury: birth trauma, tumors or cancer, or head trauma
- Disease: infection, cerebrovascular disease
- Exposure to lead or carbon monoxide

For individuals with a diagnosis of epilepsy, the following constitute some of the risk factors for seizure:

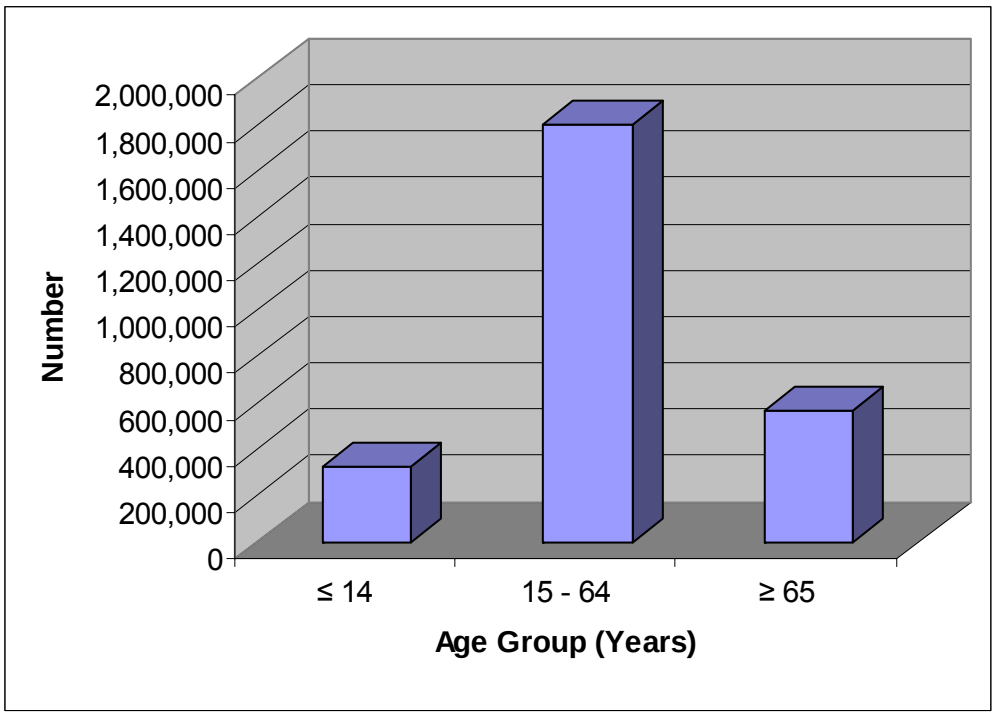
- Sleep deprivation
- Use of alcohol
- Use of illicit drugs
- Medications: some prescription and over-the-counter medications are associated with an elevated rate of seizure incidence
- Menstruation
- Missed AED doses

Epidemiology of Epilepsy

According to the most recent statistics from the Epilepsy Foundation (2005) an estimated 2.7 million people have active epilepsy[3] in the United States.(30) Figure 3 displays the number of active cases of diagnosed epilepsy in United States in 2005. According to these data, 1 percent of the general population can be expected to have a diagnosis of epilepsy by the age of 20 years and by the age of 75, this figure will have risen to approximately 3 percent. It is estimated that by the year 2050, 50 percent of new cases of epilepsy will occur in individuals over the age of 65. Overall, the prevalence of epilepsy in the US is 6 per 1,000 individuals.(21) Worldwide, epilepsy and epileptic syndromes affect > 50 million individuals, with approximately 80 percent of those affected living in the developing world.(29)

[3] Defined as a history of the disorder plus a seizure or use of an antiepileptic medicine within the past five years. It should be noted that this definition differs from that of the WHO, which states "Epilepsy is considered 'active' if the patient with epilepsy has had at least one seizure in the preceding two years, and is or has been on antiepileptic drugs for the same. Otherwise, it is termed 'inactive.'

Figure 2. Prevalence of Epilepsy in 2005 (by age group—United States(30))



The incidence of new cases of epilepsy in the United States was estimated to be 200,000 in 2005; in 70 percent of these cases, no specific underlying cause is identified.(31) The annual incidence of epilepsy in the U.S. population ranges from 30 to 57 per 100,000 individuals, with higher rates in infants and young children and in adults over 60 years of age.(31)

The Treatment of Epilepsy

Treatments for epilepsy aim at suppressing the seizures and/or epileptiform activity and reducing the severity of the seizures. The typical treatment option for epilepsy is pharmacotherapy with AEDs. Patients who do not respond well to AED therapy, or for whom AED side effects prove unmanageable, may be candidates for surgical therapy such as anterior temporal lobectomy and extra-temporal resection. NINDS estimates that approximately 80 percent of individuals diagnosed with epilepsy will achieve successful seizure control with AEDs or surgery.(24) The remaining 20 percent who continue to experience seizures despite the use of AEDs or surgery are defined as having ‘intractable epilepsy’ or ‘refractory epilepsy.’

Pharmacotherapy

Table 7 lists AEDs currently used to treat individuals with epilepsy in the United States. Included in the table are links to World Wide Web sites (primarily manufacturer’s sites) where the interested reader may obtain labeling information. Accurate and publicly available product labeling information is required by the Federal Food and Drug Administration (FDA) for any drug to be marketed in the United States. Product labeling provides details on the active agent, its dosing regimen, its indications and contraindications, and details of adverse events that have occurred (or may occur) among individuals using the medication.

Table 7. Antiepileptic Drug Treatments Currently Available in the United States

Class	Generic	Trade Names (US)	Specific Indication	Off Label Use	Link to labeling information*
Valproates	Valproate sodium	Depacon	Partial seizures with or without secondary generalization; Generalized seizures (absence) Migraine prevention; Manic episode of Bipolar Disorder	Schizophrenia; Alcohol withdrawal	http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202588.html
	Valproic acid	Depakene	Partial seizures with or without secondary generalization: Generalized seizures (absence; myoclonic; tonic-clonic) Migraine prevention; Manic episode of Bipolar Disorder	Alcohol withdrawal	http://sitesearch.abbott.com/results_rxabbott.jsp?coll=WEB_PHARMA_RxAbbott&queryText=depakene
	Divalproex sodium	Depakote	Partial seizures with or without secondary generalization; Generalized seizures (absence; myoclonic; tonic-clonic) Migraine prevention; Manic episode of Bipolar Disorder	Alcohol withdrawal	http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202588.html
	Divalproex sodium	Depakote Sprinkles	Partial seizures with or without secondary generalization; Generalized seizures (absence; myoclonic; tonic-clonic) Migraine prevention; Manic episode of Bipolar Disorder	NR	http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202588.html
Enzyme Inducing Anti-Epileptic Drugs (EIAEDs)	Phenytoin	Dilantin	Partial seizures with or without secondary generalization Generalized seizures (tonic-clonic) ; complex partial seizures; prevention of seizures secondary to neurosurgery/head trauma; control of convulsive status epilepticus	Anxiety disorders; Mood disorders; Cardiovascular complications with tricyclic antidepressant overdose; Wallenberg's syndrome; Ventricular arrhythmias; Control convulsions associated with preeclampsia; Epidermolysis bullosa	http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682022.html
	Phenobarbital	Luminal	Partial seizures with or without secondary generalization	Insomnia; nervousness; restlessness	http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682007.html
	Carbamazepine	Tegretol	Partial seizures with or without secondary generalization Generalized seizures (tonic-clonic) Trigeminal neuralgia	Antidiuretic; bipolar disorder; schizophrenia; neuralgia; glossopharyngeal neuralgia; central partial diabetes insipidus; Alcohol withdrawal	http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202111.html
	Carbamazepine	Tegretol-XR	Partial seizures with or without secondary generalization Generalized seizures (tonic-clonic) Trigeminal neuralgia	Glossopharyngeal neuralgia	http://www.pharma.us.novartis.com/product/pi/pdf/tegretol.pdf
	Carbamazepine	Carbatrol	Partial seizures with or without secondary generalization Generalized seizures (tonic-clonic)	Trigeminal neuralgia	http://www.carbatrol.com/prescribing_info.pdf
	Carbamazepine	Atretol	Partial seizures with or without secondary	Trigeminal neuralgia; bipolar disorder; schizophrenia;	http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202111

Class	Generic	Trade Names (US)	Specific Indication	Off Label Use	Link to labeling information*
			generalization Generalized seizures (tonic-clonic)	neuralgia	.html
	Carbamazepine	Epitol	Partial seizures with or without secondary generalization Generalized seizures (tonic-clonic)	Mania; acute mania, frequent episodes of mania; dysphoric mania; Trigeminal neuralgia ; Postherpetic neuralgia; Preventative treatment for bipolar disorder (manic depression); Alcohol withdrawal; Cocaine withdrawal; Abnormally aggressive behavior; Migraine	http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202111.html
GABA analogue	Gabapentin	Neurontin®	Partial seizures with or without secondary generalization Postherpetic neuralgia	Bipolar Disorder; Neuropathic pain (diabetic neuropathy, peripheral neuropathy, trigeminal neuralgia); Alcohol withdrawal; Mood stabilizer; Anxiety disorders; Depression; Insomnia; Multiple Sclerosis pain and spasticity	http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202732.html
	Gabapentin	Gabarone®	Partial seizures with or without secondary generalization Postherpetic neuralgia	Alcohol withdrawal	http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a694007.html
	Tiagabine	Gabitril®	Partial seizures with or without secondary generalization	Spasticity; Anxiety; Pain, Migraine; Bipolar Disorder	http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a698014.html
Benzodiazepines	Lorazepam	Ativan*	Status epilepticus	Amnestic; Skeletal muscle relaxant adjunct; Antianxiety agent ; Antiemetic in chemotherapy; Antipanic; Anti tremor; Sedative-hypnotic; Alcohol withdrawal	http://actmagazine.mediwire.com/main/Default.aspx?P=Content&ArticleID=312606
	Clonazepam	Klonopin Klonopin Rivotril	Generalized seizures, myoclonic	Periodic leg movements during sleep; Parkinsonian dysarthria; Acute manic episodes of Bipolar Disorder; Multifocal tic disorders; Schizophrenia; Neuralgia; Social Phobia	http://www.aesnet.org/visitors/PatientsPractice/aed/aedtable.cfm?drug=Klonopin
	Clobazam	Frisium	Generalized seizures, myoclonic	Antianxiety agent	http://www.biopsychiatry.com/clobazam.htm
	Clorazepate	ClorazeCaps® ClorazeTabs® GenZene® TransXene®	Generalized seizures, myoclonic	Antianxiety agent; Antipanic; Sedative-hypnotic	http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682052.html
	Diazepam	Valium*	Status epilepticus; severe recurrent seizure	Amnestic; Skeletal muscle relaxant adjunct; Antianxiety agent; Antipanic; Antitremor; Sedative-hypnotic; Alcohol withdrawal	http://actmagazine.mediwire.com/main/Default.aspx?P=Content&ArticleID=312606
Succinimide	Ethosuximide	Celontin Zarontin	Generalized seizures (absence; tonic-clonic)	Behavioral disorders	http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202053.html
Other antiepileptics	Felbamate	Felbatol	Partial seizures with or without secondary	Obesity	http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202711

Class	Generic	Trade Names (US)	Specific Indication	Off Label Use	Link to labeling information*
			generalization Generalized seizures (tonic-clonic associated with Lennox-Gastaut syndrome)		.html
	Pregabalin	Lyrica	Partial onset seizures; Diabetic neuropathy; Postherpetic neuralgia	Fibromyalgia; Generalized Anxiety Disorder; Social Anxiety	http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a605045.html
	Levetiracetam	Keppra	Partial seizures with or without secondary generalization; Generalized seizures (absence; myoclonic; tonic-clonic)	Migraine; Neuropathic pain; Adjunctive analgesia; Autism; Social anxiety; Tardive Dyskinesia; Myoclonus/Dystonia; Bipolar Disorder	http://www.keppra.com/hcp/Keppra_Full_PI.pdf
	Topiramate	Topamax	Partial seizures with or without secondary generalization; Generalized seizures (absence, myoclonic; tonic-clonic) Migraine	Bipolar Disorder; Alcohol withdrawal; Neuralgia; Obesity (binge eating); PTSD	http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/203085.html
	Primidone	Mysoline	Partial seizures with or without secondary generalization	Essential tremor; Congenital Long QT syndrome; Depression; Bipolar Disorder; Treatment resistant psychosis;	http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202479.html
	Lamotrigine	Lamictal LTG	Partial seizures with or without secondary generalization Acute Bipolar Disorder	Depression; schizoaffective disorder; SUNCT syndrome headaches (short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing); diabetic neuropathy; neuralgia generalized seizures (absence, myoclonic; tonic-clonic); Infantile spasms; Rett's Syndrome; startle-induced seizures	http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202786.html
	Zonisamide	Zonegran	Partial seizures with or without secondary generalization; Generalized seizures, myoclonic; tonic-clonic Adjunctive anti-seizure therapy	Tremor; Parkinson's Disease; obesity; neuropathic pain	http://www.eisai.com/pdf_files/ZonegranPIrev-1ver-1May2004.pdf
	Oxcarbazepine	Trileptal	Partial seizures with or without secondary generalization	Neuralgia	http://www.pharma.us.novartis.com/product/pi/pdf/trileptal.pdf

* Drugs listed as treatments for status epilepticus are included for the purposes of comparison
* If you are viewing this table using Microsoft Word the links are active.

Aldehydes

Aldehydes are one of the earliest antiepileptics. As paraldehyde, it was introduced into clinical practice as an antiepileptic, sedative, and treatment for alcohol withdrawal in 1882. It was also used as a hypnotic, where it remained the treatment of choice through the 1960s. Paraldehyde is still used in cases of status epilepticus because it does not suppress breathing, as can occur with other central nervous system agents.

Aromatic allylic alcohols (Stiripentol)
Approved in December 2001, this antiepileptic is used primarily in the treatment of severe myoclonic epilepsy in infancy (SMIE), also known as Dravet Syndrome. It does not appear to be effective in adolescents or adults.

Barbiturates
The central nervous system depressant phenobarbital was introduced as an antiepileptic, sedative, and hypnotic in 1912. It was the treatment of choice for epilepsy until the advent of phenytoin in 1938. Phenobarbital remained the most common hypnotic until the development of benzodiazepines in the 1960's. It is still used to treat acute convulsions or status epilepticus.

Benzodiazepines
The central nervous system depressant class of benzodiazepines acts as sedatives, hypnotics, amnestics, anxiolytics, muscle relaxants, and antiepileptics by acting on the GABA receptor $GABA_A$ to modulate higher neuronal activity. Benzodiazepines are clustered into three therapeutic groups: short acting (< 6 hours), intermediate acting (6-10 hours) and long acting (persistent effects). Benzodiazepines can accumulate in the system and result in tolerance and dependence.

Bromides
Potassium bromide was introduced as an anti-epileptic in 1857, making it the earliest effective epilepsy treatment. It was used extensively until the introduction of phenobarbital in 1912. Potassium bromide has not been approved for use in humans by the FDA.

Carboxamides

The two carboxamides of interest as antiepileptics are carbamazepine and oxcarbazepine. Initially used to treat trigeminal neuralgia (1962), carbamazepine was approved as an antiseizure medication by the FDA in 1974. It works principally via sodium channel inhibition, thus reducing the number of available open sodium channels and decreasing the excitability of brain cells.

Oxcarbazepine differs chemically from carbamazepine through the addition of an oxygen atom to the benzylcarboxamide group, which serves to reduce metabolic impact on the liver and to prevent serious anemia, which is a serious potential side effect associated with carbamazepine. It was approved by the FDA for use as an antiepileptic in 2000.

Fatty Acids

Valproates and Tiagabine are fatty acids which interact with the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Valproates act as GABA analogues, meaning they increase the amount of GABA available in the brain by converting glutamate (an excitatory neurotransmitter) into GABA. This produces an anticonvulsive effect by reducing neuron excitability and raising the threshold for seizure activity. Tiagabine (FDA approval 1997) acts to inhibit GABA uptake into the neurons and glia of the brain.

Fructose derivatives

Topiramate (1997) is a monosaccharide which acts to prevent convulsions by inhibiting excitatory neurotransmission through interactions with kainate and alpha-**a**mino-3-hydroxy-5-

methyl-4-isoxazole**p**ropionic **a**cid (AMPA) receptors, and by enhancing GABA-activated chloride channels.

GABA Analogs

The exact action in the body of antiepileptic GABA analogues is unknown. While it is effective for a variety of seizures, it is not effective for treating absence seizures. The best known gabapentin is Neurontin (Pfizer 1995). It has been estimated that approximately 90 percent of prescriptions issued for Neurontin are written for off-label purposes.

Hydantoins (Glycolylurea)

Hydantoins (the reaction product of glycolic acid and urea) act to control convulsions by reducing electrical conductivity between brain cells. Phenytoin (diphenylhydantoin) became the antiepileptic drug of choice beginning in 1938, surpassing phenobarbital in large part because it did not have the sedative effect of phenobarbital. Because of its long life in the pharmaceutical market, it is widely available as an affordable generic antiepileptic.

Pyrrolidines

The mechanism by which levetiracetam (FDA approval 1997) functions is currently unknown, but does not appear to derive from currently understood inhibitory or excitatory neural pathways.

Sulfonamides

The antiepileptic zonisamide is approved in the US as an adjunctive therapy for adult partial-onset seizures. This means that it is utilized as a way to control 'breakthrough' seizures or side effects associated with other antiepileptic medications. The exact mechanism by which zonisamide acts as an antiepileptic drug is currently not known.(32)

Surgery

Epilepsy surgery can be divided, based on the goals of the operation, into palliative and curative procedures. The primary goal of a curative surgery is for the patient to be able to lead a normal life, preferably without the use of antiepileptic medications. Examples of curative procedures include lesional resection, lobectomy, corticectomy, and some cases of hemispheric surgery and multiple subpial transections. By definition, palliative procedures only very rarely result in cessation of seizures. In patients with seizure related injuries or with a predominance of one seizure type which can be eliminated with surgery (such as drop attacks), palliation may be a desirable result. Palliative surgery may also serve to lessen the frequency or severity of seizures. Examples of palliative surgery include some cases of hemispheric surgery, multiple subpial transections, disconnection procedures including corpus callosotomy.

The goal of epilepsy surgery is either to define and resect an area of epileptogenesis or disrupt the spread of seizure activity, thus reducing the likelihood of seizures or preventing certain seizure types. Most surgical candidates suffer from partial seizures, and many have epilepsy secondary to definable structural abnormalities. The location and nature of these lesions dictates the type of surgery that will be performed and the expected outcome.

Temporal Lobe Surgery

Temporal lobe surgery is intended to eliminate complex partial seizures by removing the lesion or epileptogenic area responsible for the development of these seizures. Complex partial seizures

with or without secondary generalization are the most common seizure type associated with temporal lobe epilepsy.(33) The second most common seizure type is a simple partial seizure, which is commonly experienced as the patient's typical aura.

Temporal lobe surgery candidates constitute the largest group of epilepsy surgery patients.(34) Preoperative evaluation determines the type of lesion (tumor, vascular malformation, mesial temporal sclerosis, or other known or unknown etiology). The actual procedure depends on the location of the lesion (deep or superficial) and the extent to which tissue is to be removed.(35-37) An en bloc anterior temporal lobectomy is a standardized operative procedure in which 4.5 to 5.0 cm of the anterior lateral temporal lobe neocortex is removed along with the amygdala, the anterior aspect of the parahippocampal gyrus, and the hippocampus in the medial portion of the temporal lobe. Neocortical lesionectomy is used when the lesion, usually a tumor or vascular malformation, is contained entirely in the neocortex of the temporal lobe. Selective amygdalohippocampectomy (AH) involves the removal of the amygdala and hippocampus only. Intraoperative EEG readings may be used to "tailor" the extent of tissue resection by defining a zone of frequent interictal spiking. The use of this technique may result in more or less tissue being removed compared to the "standard" approach. Another modification to the standard approach is to remove less than 4.5 cm of the anterior temporal lobe and is referred to as "partial" resection.

Seizure free rates reported in recent systematic reviews that evaluated the effectiveness and safety of frontal lobe surgery are presented in Table 8.

Table 8. Seizure Free Rates Following Temporal Lobe Surgery: Findings of Systematic Reviews

Reference	Year	Population(s) studied	Definition of "Seizure Free"	Follow up time	% "seizure free" (95% CI)
Tellez-Zenteno et al.(38)	2005	Adults and Children	NR	Mean followup ≥5 years	66.0% (NR)
ECRI(39)	2003	Adults and children	Engel Class I ≥ 2 years	Minimum of 2 years	NR*
ECRI(39)	2003	Adults and children	Seizure-free with no auras ≥ 2 years	Minimum of 2 years	55.0% (50–60 percent)
ECRI(39)	2003	Adults and children	Seizure-free with auras ≥ 2 years	Minimum of 2 years	68.0% (65–72 %)
ECRI(39)	2003	Adults and children	Seizure-free with or without auras ≥ 2 years	Minimum of 2 years	NR*
Engel et al.(40)	2003	Adults and children	Free of seizures	Minimum of 2 years	66.8% (NR)

Corpus Callosotomy

Resection of the corpus callosum is intended as a palliative procedure that reduces the frequency of seizures that could lead to injury or seriously interfere with quality of life.(41-43) These patients typically have multifocal, unresectable, or non-localized lesions.(42) Candidates for this procedure include both children and adult patients with atonic, tonic, and tonic-clonic seizures.(42) These patients typically have daily to weekly seizures of multiple types that occur despite having therapeutic blood levels of AEDs for at least 2 years prior to surgery.(44)

Corpus callosotomy is not expected to eliminate all seizures. Individuals who undergo this procedure are very unlikely to be considered as candidates for a CMV license.

Frontal Lobe Surgery

Partial motor seizures on one side of the body are caused by lesions in the frontal lobe opposite to the side of the seizures.(45) The most common type of seizure with a frontal lobe origin begins with a turning of the head and eyes to the side opposite the lesion, often accompanied by tonic contractions of the trunk and limbs, with the potential for progression to a generalized clonic seizure. A lesion in the frontal lobe may also result in generalized convulsive seizure without the initial turning of the head and eyes. Surgery is directed at resection of the lesion.

Seizure free rates reported in recent systematic reviews that evaluated the effectiveness and safety of frontal lobe surgery are presented in Table 9.

Table 9. Seizure Free Rates Following Frontal Lobe Surgery: Findings of Systematic Reviews

Reference	Year	Population(s) studied	Definition of "Seizure Free"	Followup time	% "seizure free" (95% CI)
Tellez-Zenteno et al.(38)	2005	Adults and Children	NR	Mean follow up ≥5 years	27% (23 to 30)
ECRI(39)	2003	Adults and children	Engel Class I	Minimum of 2 years	55% to 58%
ECRI(39)	2003	Adults and children	Seizure-free with no auras	Minimum of 2 years	57%
ECRI(39)	2003	Adults and children	Seizure-free with auras	Minimum of 2 years	17% to 31%
ECRI(39)	2003	Adults and children	Seizure-free with or without auras	Minimum of 2 years	NR*

*Unexplained heterogeneity precluded authors from presenting an estimate of the % seizure free

Hemispherectomy

Hemispherectomy involves complete or partial removal of an entire cortical hemisphere of the brain including the motor and sensory cortex.(43) The intent of surgery is to eliminate seizures originating diffusely from a single cerebral hemisphere. The procedure is performed when smaller focal resections will not remove all of the epileptic region or when the progressive involvement of the remaining ipsilateral hemispheric cortex is inevitable.(46) Removal of the cortex of one hemisphere is used in patients with intractable unilateral, multifocal epilepsy associated with infantile hemiplegia or in some adults with severe cerebral disease and intractable unilateral motor seizures.(34,47) The etiological factors include injuries at birth, meningitis, acute and chronic encephalitis, head trauma, Rasmussen's syndrome, developmental dysplasia, and vascular problems.(46,48) The seizures experienced by these patients include partial motor seizures, unilateral tonic-clonic seizures, and drop attacks.(48)

Seizure free rates reported in recent systematic reviews that evaluated the effectiveness and safety of hemispherectomy are presented in Table 10.

Table 10. Seizure Free Rates Following Hemispherectomy: Findings of Systematic Reviews

Reference	Year	Population(s) studied	Definition of "Seizure Free"	Followup time	% "seizure free" (95% CI)
Tellez-Zenteno et al.(38)	2005	Adults and Children	NR	Mean followup ≥5 years	61% (54 to 68%)
ECRI(39)	2003	Adults and children	NR	Minimum of 2 years	Between 40 and 70%

Multiple Subpial Transection

Multiple subpial transection (MST) is intended for treatment-resistant patients whose epileptogenic lesion is located in cortical tissue controlling speech, movement, primary sensations, or memory.(33,49,50) Underlying etiologies include cortical dysplasia, Rasmussen's syndrome, gliosis, Landau-Kleffner syndrome, and tumors.(51-53) The procedure is designed to horizontally sever interneuronal fibers longer than 5 mm while preserving neural elements and blood vessels that are vertically oriented. Additionally, individuals who undergo MST often have surgical resection of part of the temporal and frontal lobes. This procedure is relatively new compared to the other surgical procedures for epilepsy examined in this report, with the first published account of MST appearing in 1989.(49)

Seizure-free rates reported in recent systematic reviews that evaluated the effectiveness and safety of MST are presented in Table 11.

Table 11. Seizure-Free Rates Following MST: Findings of Systematic Reviews

Reference	Year	Population(s) studied	Definition of "Seizure Free"	Followup time	% "seizure free" (95% CI)
Tellez-Zenteno et al.(38)	2005	Adults and Children	NR	Mean followup ≥5 years	16% (8 to 24%)
ECRI(39)	2003	Adults and children	Engel Class I	Minimum of 2 years	Between 20% and 57%
ECRI(39)	2003	Adults and children	Seizure-free with no auras	Minimum of 2 years	NR
ECRI(39)	2003	Adults and children	Seizure-free with auras	Minimum of 2 years	Between 37 and 57%
ECRI(39)	2003	Adults and children	Seizure-free with or without auras	Minimum of 2 years	Between 0% and 79%

The Economic Burden of Epilepsy

The economic burden of epilepsy on the U.S. economy is significant. According to Begley et al., the lifetime cost of epilepsy for an estimated 181,000 people with onset in 1995 was projected at $11.1 billion, with an estimated $12.5 billion annual cost for approximately 2.3 million prevalent cases.(54) Indirect expenditures comprised 70 percent to 85 percent of total costs with a large proportion of the costs related to productivity. Although intractable epilepsy cases (epilepsy in which seizures continue despite AED therapy) represent only 25 percent of the total disease prevalence, people with intractable epilepsy account for 79 percent of the total lifetime costs. Per capita direct medical expenditures totaled $9,593 for people with epilepsy, with indirect medical expenditures being approximately $51,662.

Epilepsy and Driving Regulations

The unpredictable nature of epileptic seizures and their consequences (sudden loss of consciousness, postural support, and bodily control) clearly presents a potential risk for a motor vehicle crash among individuals with the disorder, should a seizure occur while driving. In recognition of the potential risk to public safety, federal and state laws in the United States require that, at a minimum, epileptic seizures be 'controlled' for the individual with epilepsy to operate a motor vehicle. As would be expected, current rules and regulations for CMV drivers are far stricter.

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 commercial vehicle 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 commercial motor vehicle 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 commercial motor vehicle.
>
> (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 commercial motor vehicle;

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 commercial motor vehicle 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

Current State Regulatory Criteria for CMV Drivers

As stated at the beginning of *Current Federal Regulatory and Medical Advisory Criteria for CMV Operators* section, motor carriers engaged purely in intrastate commerce are not directly subject to FMCSRs, found in 49 CFR 301 through 399 regulations. State regulations for intrastate motor carriers must be identical to, or compatible with the Federal regulations in order for States to receive motor carrier safety grants from FMCSA.(55)

Information on regulations pertaining to intrastate CMV drivers and epilepsy on a State-by-State basis were not identified by our searches. However, state-by-state regulations pertaining to drivers of private motor vehicles were identified. Table 12 outlines the regulations and practices of U.S. states for driving and epilepsy in 2001. As shown by the table and Figure 2, there are wide disparities in driving requirements for individuals with epilepsy across the United States. Overall, 23 states have flexible driving restrictions for individuals with epilepsy.

Table 12. Driving and Epilepsy: Regulations and Practices of U.S. States*

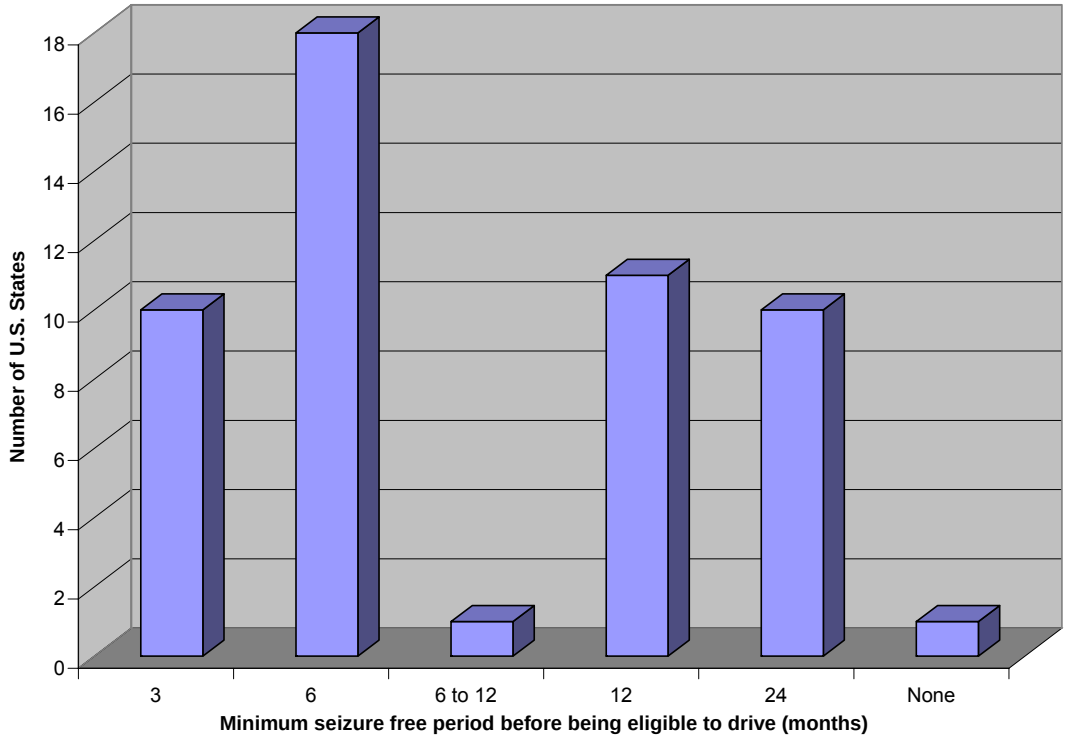
State	Legal seizure-free restriction (months)*	Rare exceptions to seizure-free interval considered based on mitigating circumstances?	Required MVA medical review (interval in years)	Mandatory physician reporting	MVA license appeal	Physician liable for driving recommendation ‡
Alabama	6	No	Annually for 5 yrs. from last seizure	No	Yes	No
Alaska	6	No	Individual	No	Yes	Yes
Arizona	3	Nocturnal, aura, and AED revision	Individual	No	Yes	No
Arkansas	12	No	Individual	No	Yes	Yes
California	3, 6, or 12	Nocturnal, breakthrough, and AED revision	Individual	Yes	Yes	Yes
Colorado	None	No	Individual	No	Yes	No
Connecticut	3*	No	Individual	No	Yes	Yes
District of Columbia	12	Nocturnal, AED revision, and solitary seizure	1 (until seizure-free for 5 yr)	No	Yes	Yes
Delaware	None	No	Individual	Yes	Yes	No
Florida	24*	Nocturnal (must supply EEG)	Individual	No	Yes	No
Georgia	12	First seizure and nocturnal	Individual	No	Yes	No

State	Legal seizure-free restriction (months)*	Rare exceptions to seizure-free interval considered based on mitigating circumstances?	Required MVA medical review (interval in years)	Mandatory physician reporting	MVA license appeal	Physician liable for driving recommendation ±
Hawaii	None	No	Individual	No	Yes	Yes
Idaho	None	MD recommendation	1 (or semi-annually)	No	Yes	No
Illinois	None	No	Individual	No	Yes	No
Indiana	None	No	Individual	No	Yes	Yes
Iowa	6	Nocturnal	6 mo. then at every renewal	No	Yes	No
Kansas	6	Nocturnal and solitary seizure	1 (until 3 yr seizure-free)	No	Yes	No
Kentucky	3	No	1	No	Yes	No
Louisiana	6	AED revision	Individual	No	No	No
Maine	3	Seizure “breakthrough”	Individual	No	Yes	No
Maryland	3	AED revision	Individual	No	Yes	Yes
Massachusetts	6*	MAB recommendation	Individual	No	Yes	Yes
Michigan	6	AED revision	Individual	No	Yes	No
Minnesota	6	Acute illness, AED revision, and first seizure	Every 6 mo. until 1 yr. seizure-free	No	Yes	No
Mississippi	12	No	Individual	No	No	No
Missouri	6	MD recommendation	Individual	No	No	No
Montana	None	No	No (MVA may require)	No	Yes	No
Nebraska	3	No	No	No	Yes	Yes
Nevada	3	MD recommendation	1 (for 3 yr)	Yes	Yes	Yes
New Hampshire	12*	MD recommendation	No	No	Yes	Yes
New Jersey	12	Neurologic MAB recommendation	Every 6 mo for 2 yr	Yes	Yes	Yes
New Mexico	12*	Nocturnal	Individual	No	Yes	No
New York	12*	AED revisions or MD recommendation	Individual	No	Yes	No
North Carolina	6-12	Nocturnal, auras, and AED revision	1	No	Yes	No

State	Legal seizure-free restriction (months)*	Rare exceptions to seizure-free interval considered based on mitigating circumstances?	Required MVA medical review (interval in years)	Mandatory physician reporting	MVA license appeal	Physician liable for driving recommendation ‡
North Dakota	6*	No	1 (at least 3 yr)	No	Yes	No
Ohio	None	No	6 and 12 mos, then annually	No	Yes	No
Oklahoma	12	Nocturnal	MVA determines	Yes	Yes	No
Oregon	6*	Nocturnal, auras, AED revision, and acute illness	Individual	Yes	Yes	Yes
Pennsylvania	6	Nocturnal, auras, AED revision, and acute illness	Individual	No	Yes	No
Rhode Island	None	MAB recommendation	Yes	No	Yes	No
South Carolina	6	No	6 mo, then 3 yr annually	No	Yes	No
South Dakota	12*	No	Every 6 mo. until seizure-free	No	Yes	Yes
Tennessee	6	No	At discretion of MAB	No	Yes	Yes
Texas	6	AED revision	1	No	Yes	No
Utah	3*	Yes	6 mo until seizure-free 1 yr	No	Yes	No
Vermont	None	No	Individual	Yes	Yes	Yes
Virginia	6	Nocturnal, aura, AED revision, and acute illness	Individual	No	Yes	No
Washington	6	MD recommendation	Individual	No	Yes	Yes
West Virginia	12	Nocturnal, aura, AED revision, and acute illness	Individual	No	Yes	No
Wisconsin	3	No	6 mo for 2 yr	No	Yes	No
Wyoming	3	Nocturnal	1	No	Yes	Yes

Adapted from Krauss et al.(56)
*Seizure-free restriction frequently adjusted by MVA MAB and treating physicians
†Mitigating factors considered in permitting some patients to drive despite less than minimum seizure-free period: auras, nocturnal seizures only seizure breakthrough during physician-directed AED change, and solitary or first seizure.
‡No = physicians legally immune or indemnified; yes = physician possibly liable for driving recommendation
MVA: motor vehicle agency; AED antiepileptic drugs; MAB: Medical Advisory Board

Figure 2. Minimum Seizure-Free Period Requirements for Driving a Private Motor Vehicle from U.S. States



Current Regulatory and Medical Advisory Criteria from other Countries

Regulatory standards and guidance pertaining to cardiovascular disease and commercial motor vehicle driving in Australia, Canada, and the United Kingdom are presented in Table 13.

Table 13. Regulatory and Medical Advisory Criteria from other Countries

Condition	Australia	Canada	UK
Single provoked or unprovoked seizure	The criteria for an unconditional license are NOT met: • If the person has had a seizure due to any cause. A *conditional license* may be granted by the Driver Licensing Authority taking into account the opinion of a specialist in epilepsy and the size and condition of the vehicle, the duties to be performed and the hours to be worked (with conditions that may include limited and/or restricted use): • If the person has had a single provoked seizure event; and • Provocative factors can be avoided reliably; and • Has been seizure free for one year; and • Takes no anti-epileptic	Neurologic assessment, including EEG (awake and asleep) and appropriate imaging must be performed If no epilepsy diagnosis, resume professional driving if seizure free for 12 months	Following a first unprovoked seizure, drivers must demonstrate 10 years freedom from further seizures, without anticonvulsant medication in that time. Following a solitary seizure associated with either alcohol or substance misuse or prescribed medication, a 5 year period free of further seizures, without anticonvulsant medication in that time, is required. If there are recurrent seizures, the epilepsy regulations apply.

Condition	Australia	Canada	UK
	medication; and • The EEG shows no epileptiform activity. OR Taking into account the size and condition of the vehicle, the duties to be performed and the hours to be worked (with conditions including limited and/or restricted use): • If the person has had a single provoked seizure event; and • Provocative factors can be avoided reliably; and • Has been seizure free for one year; and • Takes no anti-epileptic medication; and • The EEG shows no epileptiform activity.		
≥2 unprovoked seizures or diagnosed with epilepsy following single unprovoked seizure	The criteria for an unconditional license are NOT met: • If the person has epilepsy. A *conditional license* may be granted by the Driver Licensing Authority taking into account the opinion of a specialist in epilepsy (who may recommend variation of the seizure-free periods in exceptional circumstances), and the nature of the driving task, and subject to periodic review: • If the person has a past history of febrile seizures or of benign childhood epilepsy; and • Does not take anti-epileptic medication; and • The EEG shows no epileptiform activity. OR • If the person has a past history of a single seizure event; or of seizures occurring only under provocative circumstances that can be avoided reliably; and • Has been seizure free for five years; and • Takes no anti-epileptic medication; and • The EEG shows no epileptiform activity awake. OR • If the person has epilepsy and is taking anti-epileptic medication; and • Maintains at least annual review and compliance; and • Has been seizure free for five years; and • Has had no more than three seizures in the preceding ten	Individual qualifies if they have been seizure free for at least 5 years (Recommendations for individual patients may differ on an exceptional basis.)	Regulations require a driver to remain free of epileptic attacks for at least 10 years without anticonvulsant medication in that time.

Condition	Australia	Canada	UK
	years; and • The EEG shows no epileptiform activity. Taking into account the size and condition of the vehicle, the duties to be performed and the hours to be worked (with conditions including limited and/or restricted use): • If the person has epilepsy and is taking anti-epileptic medication; and • Maintains periodic review and compliance; and • Has been seizure free for five years; and • The EEG shows no epileptiform activity.		
After surgery to prevent epileptic seizures	A *conditional license* may be granted by the Driver Licensing Authority taking into account the opinion of a specialist in epilepsy (who may recommend variation of the seizure-free periods in exceptional circumstances), and the nature of the driving task, and subject to periodic review: • If the person has epilepsy and has had surgical treatment; and • Maintains at least annual review; and • Has been seizure free for five years; and • The EEG shows no epileptiform activity.	An individual qualifies if 5 years seizure free (Recommendations for individual patients may differ on an exceptional basis).	Not specifically addressed
Seizures only in asleep or immediately on wakening	Not specifically addressed	An individual qualifies if 5 years seizure free (Recommendations for individual patients may differ on an exceptional basis).	Not specifically addressed
Initial withdrawal or change in AED	Withdrawal of medication is not compatible with continued driving of commercial vehicles.	An individual cannot drive for 6 months from the time medication is discontinued or changed. If seizures occur, general epilepsy rules apply	If an epileptic seizure does occur, the patient/driver will need to satisfy driving license legislation before resuming driving and will need to be counseled accordingly. The UK Secretary of State's Honorary Medical Advisory Panel on Driving and Disorders of the Nervous System recommends that patients should be warned of the risk they run, both of losing their driving license and also of having a seizure which could result in a road traffic accident. The Panel advises that patients should be advised not to drive from commencement of the period of withdrawal and thereafter for a period of 6 months after cessation of treatment.
If seizures recur after withdrawal or change	Not specifically addressed	Resume driving if seizure free for 6 months (Recommendations for individual patients may differ on an exceptional basis.)	Not specifically addressed

Condition	Australia	Canada	UK
Long-term withdrawal and discontinuation of medication	Not specifically addressed	An individual qualifies if seizure free off medication for 5 years with no epileptiform activity within previous 6 months on waking and sleep EEG	Not specifically addressed
Auras (simple partial seizures)	Not specifically addressed	Individual may drive if: • Seizures remain benign for at least 3 years • No generalized seizures • Neurologist approves • No impairment in level of consciousness or cognition • No head or eye deviation with seizures	Not specifically addressed
Alcohol-withdrawal induced seizures	Not specifically addressed	An individual qualifies if: • Remain alcohol free and seizure free for 6 months • Complete a recognized rehabilitation program for substance dependence • Compliant with treatment	Not specifically addressed
Post-traumatic seizures (single, not epilepsy)	Not specifically addressed	Same as for single, unprovoked seizure	Not specifically addressed
Juvenile myoclonic epilepsy (Janz syndrome)	Not specifically addressed	No driving of any class of vehicle unless taking appropriate anti-seizure medication	Not specifically addressed
Injury or neurological disorder known to be a risk factor for seizure or epilepsy	Not specifically addressed	Not specifically addressed	In all cases where a "liability to epileptic seizures" either primary or secondary has been diagnosed the specific epilepsy regulation for this group must apply. The only exception to this is for a seizure occurring immediately at the time of the acute head injury or intracranial surgery, and not thereafter and/or where no liability to seizure has been demonstrated. Following head injury or intracranial surgery, the epilepsy risk must fall to 2% per annum or less before returning to vocational driving.

Medical Fitness Standards and Guidelines for Individuals Performing Transportation Safety in the United States

In this section we summarize the current medical fitness standards and guidelines for individuals performing other forms of transportation safety in the United States.

Aeronautics and Space

Federal Aviation Authority (FAA) regulations that pertain to neurological disorders consist of the following articles (available at the US government website: http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=cf5516738c4b80532a175b611bfefd0d&rgn=div5&view=text&node=14:2.0.1.1.5&idno=14) :

Applicant History - Item 18. Medical History
l. Neurological disorders; epilepsy, seizures, stroke, paralysis, etc.

The applicant should provide history and treatment, pertinent medical records, current status report and medication. The Examiner should obtain details about such a history and report the results. An established diagnosis of epilepsy, a transient loss of control of nervous system function(s), or a disturbance of consciousness is a basis for denial no matter how remote the history. Like all other conditions of aeromedical concern, the history surrounding the event is crucial. Certification is possible if a satisfactory explanation can be established.

Exam Techniques and Criteria for Qualification.
Item 46. Neurologic Code of Federal Regulations
Title 14: Aeronautics and Space
PART 67—MEDICAL STANDARDS AND CERTIFICATION
Subpart B—First-Class Airman (Commercial Pilots, Airline Transport Pilots) Medical Certificate

67.109 Neurologic.

Neurologic standards for a first-class airman medical certificate are:

(a) No established medical history or clinical diagnosis of any of the following:

(1) Epilepsy;

(2) A disturbance of consciousness without satisfactory medical explanation of the cause; or

(3) A transient loss of control of nervous system function(s) without satisfactory medical explanation of the cause.

(b) No other seizure disorder, disturbance of consciousness, or neurologic condition that the Federal Air Surgeon, based on the case history and appropriate, qualified medical judgment relating to the condition involved, finds—

(1) Makes the person unable to safely perform the duties or exercise the privileges of the airman certificate applied for or held; or

(2) May reasonably be expected, for the maximum duration of the airman medical certificate applied for or held, to make the person unable to perform those duties or exercise those privileges.

The medical standards and certification for Subpart B – First Class Airman are identical for the following categories noted by the FAA

Subpart C—Second-Class Airman (Commercial, non-airline duties such as crop dusters, charter pilots and corporate pilots) Medical Certificate (§ 67.209 Neurologic)

Subpart D—Third-Class Airman (Private pilots only) Medical Certificate (§ 67.309 Neurologic)

Examination Techniques:-Item 46. Neurologic

A neurologic evaluation should consist of a thorough review of the applicant's history prior to the neurological examination. The Examiner should specifically inquire concerning a history of weakness or paralysis, disturbance of sensation, loss of coordination, or loss of bowel or bladder

control. Certain laboratory studies, such as scans and imaging procedures of the head or spine, electroencephalograms, or spinal paracentesis may suggest significant medical history. The Examiner should note conditions identified in Item 60 on the application with facts, such as dates, frequency, and severity of occurrence.

A history of simple headaches without sequela is not disqualifying. Some require only temporary disqualification during periods when the headaches are likely to occur or require treatment. Other types of headaches may preclude certification by the Examiner and require special evaluation and consideration (e.g., migraine and cluster headaches).

One or two episodes of dizziness or even fainting may not be disqualifying. For example, dizziness upon suddenly arising when ill is not a true dysfunction. Likewise, the orthostatic faint associated with moderate anemia is no threat to aviation safety as long as the individual is temporarily disqualified until the anemia is corrected.

An unexplained disturbance of consciousness is disqualifying under the medical standards. Because a disturbance of consciousness may be expected to be totally incapacitating, individuals with such histories pose a high risk to safety and must be denied or deferred by the Examiner. If the cause of the disturbance is explained and a loss of consciousness is not likely to recur, then medical certification may be possible.

The basic neurological examination consists of an examination of the 12 cranial nerves, motor strength, superficial reflexes, deep tendon reflexes, sensation, coordination, mental status, and includes the Babinski reflex and Romberg sign. The Examiner should be aware of any asymmetry in responses because this may be evidence of mild or early abnormalities. The Examiner should evaluate the visual field by direct confrontation or, preferably, by one of the perimetry procedures, especially if there is a suggestion of neurological deficiency.

Application Review
Item 60. Comments on History and Findings

Comments on all positive history or medical examination findings must be reported by Item Number. Item 60 provides the Examiner an opportunity to report observations and/or findings that are not asked for on the application form. Concern about the applicant's behavior, abnormal situations arising during the examination, unusual findings, unreported history, and other information thought germane to aviation safety should be reported in Item 60. The Examiner should record name, dosage, frequency, and purpose for all currently used medications.

If possible, all ancillary reports such as consultations, electrocardiograms (ECGs), x-ray release forms, and hospital or other treatment records should be attached. If the delay for those items would exceed 14 days, the Examiner should forward all available data to the Aerospace Medical Certification Division (AMCD), with a note specifying what additional information is being prepared for submission at a later date.

If there are no significant medical history items or abnormal physical findings, the Examiner should indicate this by checking the appropriate block.

Aerospace Medical Dispositions:-Item 46. Neurologic

A history or the presence of any neurological condition or disease that potentially may incapacitate an individual should be regarded as initially disqualifying. Issuance of a medical certificate to an applicant in such cases should be denied or defer, pending further evaluation. A convalescence period following illness or injury may be advisable to permit adequate stabilization of an individual's condition and to reduce the risk of an adverse event. Applications from individuals with potentially disqualifying conditions should be forwarded to the AMCD.

Processing such applications can be expedited by including hospital records, consultation reports, and appropriate laboratory and imaging studies, if available. Symptoms or disturbances that are secondary to the underlying condition and that may be acutely incapacitating include pain, weakness, vertigo or in coordination, seizures or a disturbance of consciousness, visual disturbance, or mental confusion. Chronic conditions may be incompatible with safety in aircraft operation because of long-term unpredictability, severe neurologic deficit, or psychological impairment.

The most common conditions of aeromedical significance and course of action that should be taken by the medical examiner are presented below:

- Cerebrovascular Disease (including the brain stem)
- Demyelinating Disease
- Extrapyramidal, Hereditary, and Degenerative Diseases of the Nervous System
- Headaches
- Hydrocephalus and Shunts
- Infections of the Nervous System
- Neurologic Conditions
- Other Conditions
- Presence of any neurological condition or disease that potentially may incapacitate an individual
- Spasticity, Weakness, or Paralysis of the Extremities
- Vertigo or Disequilibrium

Medical certificates must not be issued to an applicant with medical conditions that require deferral, or for any condition not listed that may result in sudden or subtle incapacitation without consulting the AMCD or the Regional Flight Surgeon (RFS). Medical documentation must be submitted for any condition in order to support an issuance of an airman medical certificate.

Merchant Mariners

Federal regulatory guidelines (not standards) for merchant mariners regarding neurological disorders consist of the following articles administered by the US Department of Transportation (http://www.uscg.mil/hq/g-m/nvic/2_98/n2-98.pdf):
Title 46, Parts 10, 12, and 13 of the regulatory guidelines require individuals to be physically qualified to hold certain merchant mariner's licenses and documents. With the exception of visual acuity and color vision these regulatory requirements are not specified. Potentially

disqualifying neurologic conditions for deck officers, engineer officers, pilots, and original or renewal of Merchant Mariner Document (MMD) (except for entry level ratings) consist of:

- Any convulsive disorder resulting in an altered state of consciousness regardless of control by medication requires further evaluation.
- Any condition with seriously limited balance or coordination (e.g. Parkinson's disease, chorea, Ménière's disease)
- Neurosyphilis
- Narcolepsy
- Senility
- Somnambulism

Railroads

With the exception of federally regulated examinations for vision, color vision, and hearing, US railroads have discretion as to the content, frequency, and extent of their medical screening programs. A review of the current approaches used by representative Class I, short line/regional and commuter railroads reveal no specific medical guidelines addressing neurological conditions. In addition, not all of these railways required self-reporting of medical conditions or medication use. Table 14 provides information on the companies included in the review:

Table 14. Railway Companies Requiring Self-Reporting of Medication Use

Railway	Self-Reporting Required (Y/N/Not Reported)	Self-Reporting of Medication Use Required (Y/N/Not Reported)
Burlington Northern Santa Fe Railway	Y	NR
CSX Transportation	NR	Y
Kansas City Southern	N	Y
Norfolk Southern	Y	Y – Depending on position
Union Pacific	Y	N
Metro-North Railroad	Y	Y
NJ Transit	N	Y
Belt Railway of Chicago	N	Y - Part of a Drug Test Policy
Florida East Coast Railway	N	Y
Montana Rail Link	Y - Only if results in lost work time	Y - Part of a Drug Test Policy
Rail America	NR	N
Holding Company (fictional name)	N	Y – Only if taking part in Drug Screening Test

A 1998 FRA Safety Advisory, Safe Use of Prescription and Over-the-Counter Drugs, 63 Federal Regulation 71334 (1998) recommends that railroads use the same guidelines when considering the use of prescription or over-the-counter medication as would be used when reviewing controlled substances.

Methods

The *Methods* section provides a synopsis of how we identified and analyzed information for the report. The section briefly covers the key questions addressed, literature searches performed, the criteria used including studies, evaluation of study quality, assessment of the strength of the evidence base for each key question, and the methods used for abstracting and analyzing available data. Specific details of literature searches, study quality assessment, statistical approaches used, etc. are documented in appendices.

Key Questions

This evidence report addresses six key questions. These key questions, which were developed by FMCSA in collaboration with ECRI, are listed below:

Key Question 1: Are individuals with seizure disorders (epilepsy) at an increased risk for a motor vehicle crash when compared to 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[4] effects of an AED on surrogate markers of driver safety among individuals with recurrent seizure disorders? Surrogate markers of driver safety consist of the following:

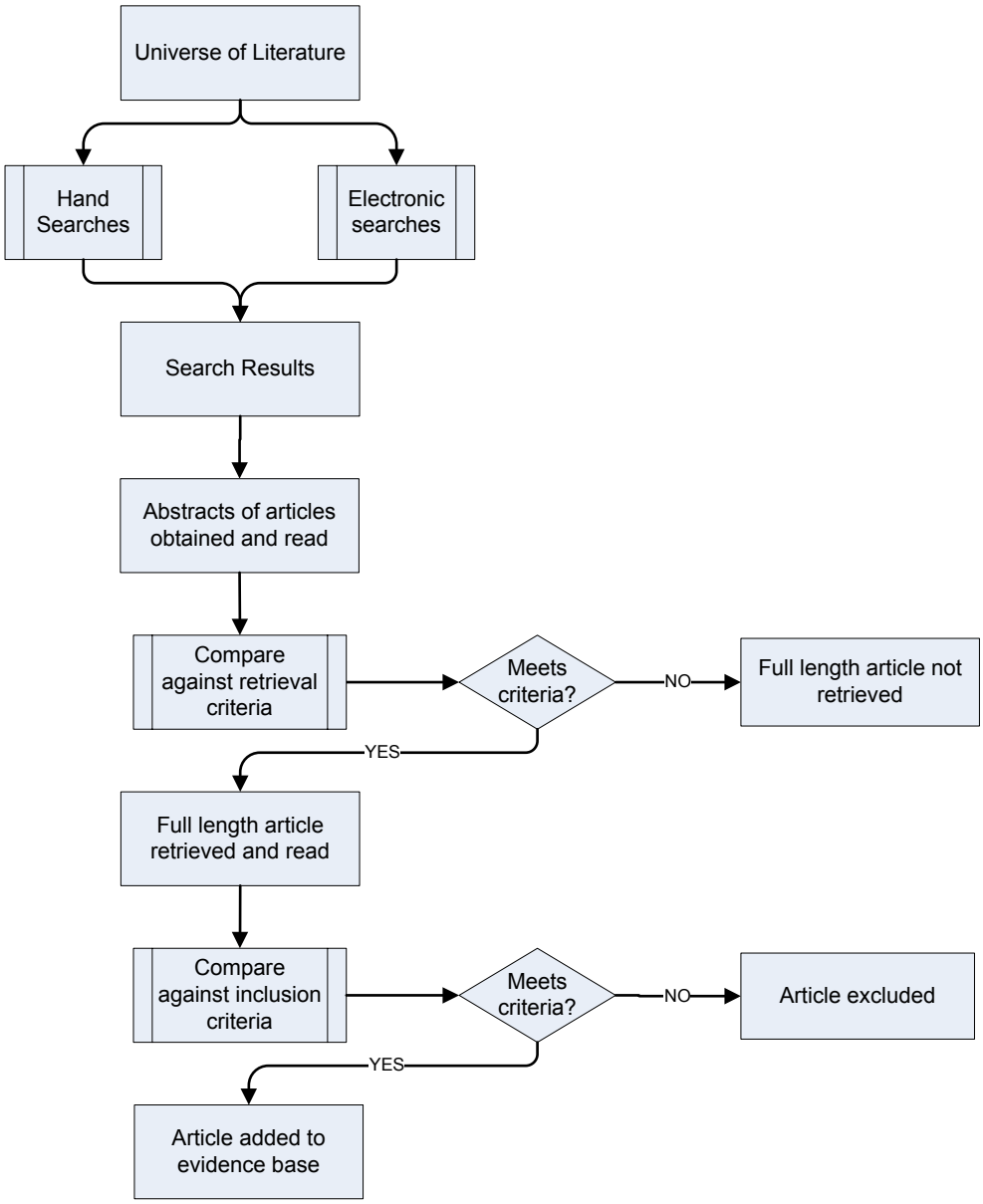
c) Driving performance (simulated or closed course)
d) Cognitive and psychomotor function

Identification of Evidence Bases

The individual evidence bases for each of the six key questions addressed in this evidence report were identified using the multistaged process captured by the algorithm presented in Figure 3. The first stage of this process consists of a comprehensive search of the literature. The second stage of the process consists of the examination of abstracts of identified studies in order to determine which articles will be retrieved. The final stage of the process consists of the selection of the actual articles that will be included in the evidence base.

[4] >2 weeks treatment

Figure 3. Evidence Base Identification Algorithm



Searches

One characteristic of a good evidence report is a systematic and comprehensive search for information. Such searches distinguish systematic reviews from traditional literature reviews which use a less rigorous approach to identifying and obtaining literature thereby allowing a reviewer to include only articles that agree with a particular perspective and to ignore articles that do not. Our approach precludes this potential reviewer bias because we obtain and include articles according to explicitly determined *a priori* criteria. Details of the search strategies used in this report are presented in Appendix A.

Electronic Searches

We performed comprehensive searches of the electronic databases listed in Table 15.

Table 15. Electronic Databases Searched

Name of database	Date limits	Platform/provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	Through February 5th 2007	OVID
Cochrane Library	Through February 5th 2007	www.thecochranelibrary.com
Embase (Excerpta Medica)	Through February 5th 2007	OVID
Medline	Through February 5th 2007	OVID
PubMed (Pre Medline)	Through February 5th 2007	www.pubmed.gov
TRIS Online (Transportation Research Information Service Database)	Through February 5th 2007	http://trisonline.bts.gov/search.cfm
PsycINFO	Through February 5th 2007	
United States National Guideline Clearinghouse™ (NGC™)	Through February 5th 2007	
Health Technology Assessment Database (HTA)	Through February 5th 2007	

Manual Searches

We reviewed journals and supplements maintained in ECRI's collections of more than 1,000 periodicals. Non-journal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. In addition, we examined the reference lists of all obtained articles with the aim of identifying relevant reports not identified by our electronic searches. In order to retrieve additional relevant information, we also performed hand searches of the "gray literature." Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These latter documents do not appear in the peer-reviewed journal literature.

Retrieval Criteria

Retrieval criteria were used to determine whether a full-length version of an article identified by our searches should be ordered. Decisions pertaining to whether a full-length article should be retrieved are usually based on a review of available abstracts. For this project, retrieval criteria were determined *a priori* in conjunction with FMCSA. The retrieval criteria are presented in Appendix B.

If an article did not meet the retrieval criteria for this evidence report, the full-length version of the article was not obtained. If it was unclear whether a potentially relevant article met our retrieval criteria (e.g. no abstract was available for evaluation), the full-length version of that article would be obtained.

Inclusion and Exclusion Criteria

Each retrieved article was read in full by an ECRI analyst who determined whether that article met a set of predetermined, question specific, inclusion criteria. As was the case for the retrieval criteria, the inclusion and inclusion criteria for this evidence report were determined *a priori* in conjunction with FMCSA. These inclusion and exclusion criteria are presented in Appendix C.

If on reading an article it was found not to meet the question specific inclusion criteria listed in Appendix C, the article was excluded from the analysis. Each excluded article, along with the reason(s) for its exclusion, are presented in Appendix D.

Evaluation of Quality of Evidence

Rather than focus on the quality of the individual studies that comprise an evidence base, our approach to assessing the quality of evidence focused on the overall *body* of the available evidence that was used to draw an evidence-based conclusion.(57) Using this approach, which is described briefly in Appendix E, we took into account not only the quality of the individual studies that comprise the evidence base for each key question, we will also consider the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Our approach to assessing the strength of the body of evidence makes a clear distinction between a qualitative conclusion (e.g. Individuals with epilepsy are at increased risk for a motor vehicle accident) and a quantitative conclusion (e.g. When compared to individuals without epilepsy, the relative risk for a motor vehicle crash among individuals with epilepsy who require AEDs is 1.47 (95 percent CI: 1.03–1.74; $P<0.005$). As shown in Table 16, we will assign a separate strength of evidence rating to each of type of conclusion. Evidence underpinning a qualitative conclusion will be rated according to its strength, and evidence underpinning quantitative conclusions will be rated according to the stability of the effect size estimate that is calculated.

Table 16. Strength of Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion	
Strong	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	
High	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.
Moderate	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	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.

Strength of Evidence	Interpretation
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.

The definitions presented in the table above are intuitive. Qualitative conclusions that are supported by strong evidence are less likely to be overturned by the publication of new data than conclusions supported by weak evidence. Likewise, quantitative effect size estimates that deemed to be stable are more unlikely to change significantly with the publication of new data than are unstable effect size estimates.

Methodological Issues Specific to the Study of Epilepsy

There are a number of methodological issues that must be considered in a systematic review of epilepsy studies. In 1993 the Commission on Epidemiology and Prognosis, International League Against Epilepsy published a set of guidelines for the epidemiological study of epilepsy which highlighted many of the problems which will be mentioned in the sections pertaining to each of the key questions addressed in this report:

> *"..published results are often discordant, even in simple descriptive studies, because of lack of agreement regarding the most basic concepts. Definitions of epilepsy, seizures, and independent variables often are not elaborated. The classification of seizures (Commission, 1981) and epileptic syndromes (Commission 1989) proposed by the International League Against Epilepsy are either not used or are used incorrectly. Analysis of risk factors is also a source of confusion, and basic epidemiologic measures are frequently misstated ... lack of standardized definitions, differences in methods of case ascertainment, diagnostic accuracy, and seizure classification impede meaningful comparison."*(58)

Vermeulen and Aldenkamp noted that the comparison between studies on epilepsy was complicated by population heterogeneity, including mixed populations of children and adults; mixed populations of the newly diagnosed and chronic AED users; the wide variety of assessment tools used to establish the effects of AED use; and choice of study design which implicitly looked for large treatment effects.(59) These criticisms were echoed in a review by Dodrill, where he noted that observed problems such as selection bias, the impact of seizure on performance, and lack of appropriate statistical power could all affect the findings of a study.(60)

Additional challenges to the study of epilepsy include heterogeneity between types of seizures experienced in the population of interest (generalized seizures vs. partial complex seizures), seizure frequency, lack of agreement on nomenclature and definitions (i.e. remission and recurrence/relapse), mixing of etiologies (the combined use of data from individuals with provoked seizures and unprovoked seizures), and the mixing of individuals with controlled epilepsy and those with refractory epilepsy in the same base population.

Statistical Methods

The set of analytic techniques used in this report is extensive (Appendix B). In summary, random- and fixed-effects meta-analyses were used to pool data from different studies.(1,3,3,4,4,5,61,62) Important differences in the findings of different studies (heterogeneity) were identified using the Q-statistic and I^2.(6,7,7,8,8,61,63-65) Whenever appropriate, heterogeneity was explored using meta-regression techniques.(66-68) Sensitivity analyses, aimed at testing the robustness of our findings, were performed using cumulative fixed- and random-effects meta-analyses.(9-11,69-72) The presence of publication bias was tested for using the "trim and fill" method.(12-14,73) All meta-analyses in this Evidence Report were performed using Comprehensive Meta-Analysis software.(12-14)

We calculated several different estimates of effect. The choice of effect size estimate depended on the purpose of the studies we assessed, their design, and whether reported outcome data were continuous or dichotomous. Between-group differences in outcome measured using continuous data were analyzed in their original metric (if all included studies reported on the same outcome using the same metric) or data were standardized into a common metric known as the standardized mean difference (SMD). Dichotomous data were analyzed using the rate ratio (RR) or the odds ratio (OR). The formulae for these effect sizes and their variance are presented in Table 17. If means and standard deviations were not available for continuous data, every effort was made to determine an estimate of treatment effect from reported statistics (e.g., t-values, f-values) or from p-values using methods described in detail elsewhere.(74)

Table 17. Effect Size Estimates Used in Evidence Report and their Variance

Effect size	Formula (Effect size)	Formula (Variance)
WMD	$\mu_{TG}-\mu_{CG}$	$\left(\sqrt{\frac{(n_{TG}-1)(s_{TG})^2+(n_{CG}-1)(s_{CG})^2}{n_{TG}+n_{CG}-2}}\right)\left(\frac{1}{n_{TG}}+\frac{1}{n_{eg}}\right)$
SMD	$\frac{\mu_{TG}-\mu_{CG}}{\left(\sqrt{\frac{(n_{TG}-1)(s_{TG})^2+(n_{CG}-1)(s_{CG})^2}{n_{TG}+n_{CG}-2}}\right)}$	$\frac{n_{TG}+n_{CG}}{n_{TG}n_{CG}}+\frac{SMD^2}{2(n_{TG}+n_{CG})}$
Where: μ_{TG} = mean (treatment group); μ_{CG} = mean (control group); s_{TG} = standard deviation (treatment group); s_{CG} = standard deviation (control group); n_{TG} = enrollees (treatment group); n_{CG} = enrollees (control group)		
Event Rate	$a/a+b$	$\ln\left[\frac{1}{a}+\frac{1}{a+b}\right]$
Where: a = number of individuals in cohort experiencing an event; b = number of individuals in cohort who did not experience an event		
RR (incidence)	$\left(\frac{a_{CVDs}}{pt_{CVD}}\right)\Big/\left(\frac{b_{control}}{pt_{control}}\right)$	$\ln\left[\frac{1}{a_{CVD}}+\frac{1}{b_{control}}\right]$

Effect size	Formula (Effect size)	Formula (Variance)
Where: a = number of individuals with CVD who crashed; pt_{CVD} = rate denominator (CVD grp); b = number of individuals without CVD who crashed; $pt_{control}$ = rate denominator (control grp)		
OR	$\left(\frac{a}{b}\right) \Big/ \left(\frac{c}{d}\right) = \left(\frac{ad}{bc}\right)$	$\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}$
RR	$\left(\frac{a}{a+c}\right) \Big/ \left(\frac{b}{b+d}\right)$	$\frac{1}{a}+\frac{1}{a+c}+\frac{1}{b}+\frac{1}{b+d}$
Where: a = number of individuals with CVD who crashed; b = number of individuals without CVD who crashed; c = number of individuals with CVD who did not crash; d = number of individuals without CVD who did not crash.		

CVD = cardiovascular disease; RR = rate ratio; OR = Odds Ratio; RR = rate ratio; SMD = standardized mean difference; WMD = weighted mean difference

If means and standard deviations were not available for continuous data, every effort was made to determine an estimate of treatment effect from reported statistics (e.g., t-values, f-values) or from p-values using methods described in detail elsewhere.(74)

Time-to-event (survival) data were pooled using non-linear regression techniques. This method is similar to that utilized by Shore et al. who combined survival curves from 24 studies by assuming that the survival curves reported by each study took the form of an exponential decay curve.(75) A simulation study of this method found that this method produced "reasonably accurate" summary survival curves.(76) The method used in this evidence report differs from that used by Shore in that we did not simply assume that the survival data extracted from the included studies was best described by an exponential decay function. Rather, we determined the function that best fit data extracted from each included study by fitting mathematical models based on several plausible probability distributions (exponential, Weibull, etc). We then tested the goodness of fit of the resulting survival functions to the available data and chose the model that best described these data. Relevant parameters that described each resulting mathematical function (and their 95 percent confidence intervals) were then pooled as described above.

Synthesis of Results

This section summarizes the findings of our analyses for each of the five key questions that we addressed.

Key Question 1: Are individuals with epilepsy at increased risk for a motor vehicle crash when compared to comparable individuals who do not have epilepsy?

Introduction

The unpredictable nature of epileptic seizures and their consequences (sudden loss of consciousness, postural support, and bodily control) presents a potential risk for a motor vehicle crash among individuals with the disorder, should a seizure occur while driving. While there is no doubt that experiencing a seizure while driving can result in a crash,[5] evidence demonstrating that crash rates among the population of individuals with epilepsy are higher than expected among individuals who do not have the disorder is not so clear cut. Several reviews of the literature have noted that the available literature on the risk for a motor vehicle crash associated with epilepsy is inconsistent.(77-82,83)

To date, no review of the literature has attempted to formally assess the available evidence quantitatively using the methodology of systematic review and meta-analysis. In addressing Key Question 1, we use these methods with the aim of empirically determining whether individuals with epilepsy are at a higher risk for a crash than individuals who do not have the disorder and, if such an increased risk is observed, to quantify the magnitude of this excess risk.

Identification of Evidence Base

The identification of the evidence base for Key Question 1 is summarized in Figure 9. Our searches[6] identified a total of 126 articles that appeared to be relevant to this key question. Following application of the retrieval criteria[7] for this question, 51 full-length articles were retrieved and read in full. Of these 51 retrieved articles, nine articles were found to meet the inclusion criteria[8] for Key Question 1. Table D-1 of Appendix D lists the 42 articles that were retrieved but then excluded and provides rationale for their exclusion. Table 30 lists the nine articles that met the inclusion criteria for Key Question 1.

[5] Numerous examples of seizure related accidents exist.
[6] See Appendix A for search strategies
[7] See Appendix B for retrieval criteria
[8] See Appendix C for inclusion criteria

Figure 4. Development of Evidence Base for Key Question 1

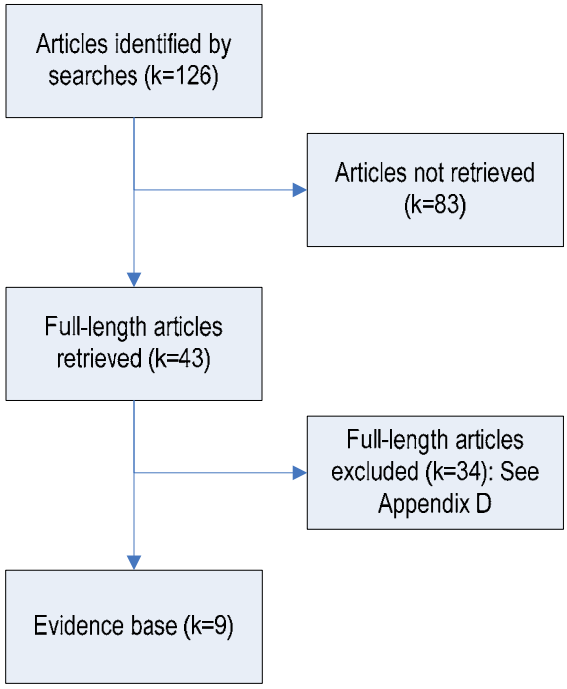


Table 18. Evidence Base for Key Question 1

Reference	Year	Study Location	Country
Sheth et al.(84)	2004	Entire USA	USA
Vernon et al.(85)	2002	State of Utah	USA
Lings(86)	2001	Odense	Denmark
Taylor et al.(87)	1996	Nationwide	UK
Hansotia et al.(88)	1991	Wisconsin	USA
Popkin and Waller(89)	1989	North Carolina	USA
Davis et al.(90)	1973	Oklahoma	USA
Crancer and McMurray(91)	1968	Washington	USA
Waller(92)	1965	California	USA

Evidence Base

This subsection provides a brief description of the main attributes of the nine studies that comprise the evidence base for Key Question 1. Here we discuss information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of

commercial vehicles. Detailed information on the design, conduct and findings of each of the included studies is presented in the *Study Summary Tables* of Appendix G.

Characteristics of Included Studies

The primary characteristics of the nine included studies that address Key Question 1 are presented in Table 19.

Table 19. Key Study Design Characteristics of Studies that Address Key Question 1

Reference	Year	Design (prospective or retrospective)	Comparison	Definition of epilepsy used	Subtype(s) of epilepsy or seizure	Driving exposure controlled for?	Primary outcome	Outcome self-reported?
Sheth et al.(84)	2004	Case-control (retrospective)	Estimated 1,000,535 individuals with an estimated 196,183,333 individuals in total population*	Individuals with a primary or secondary ICD-9 diagnosis of epilepsy (codes 345 to 345.9) or syncope (code 780.3)†	NR	No	Difference in fatal crash rate	No
Vernon et al.(85)	2002	Case-control (retrospective)	2,739 individuals with epilepsy† with 2,739 individuals without epilepsy matched for age, sex, and place of residence	Epilepsy or other episodic conditions including syncope, cataplexy, narcolepsy, hypoglycemia, and episodic vertigo that interferes with function†	NR	No	Difference in crash rate	No
Lings(86)	2001	Case-control (retrospective)	159 individuals with epilepsy compared with 559 individuals without epilepsy matched for age, sex, place of residence, and exposure period	Individuals with a primary or secondary ICD-8 diagnosis of epilepsy	NR	No	Difference in crash rate	No
Taylor et al.(87)	1996	Case-control (retrospective)	16,958 drivers with epilepsy compared with 8888 individuals without epilepsy. Data adjusted for differences in age, sex, driving experience, and mileage driven	Seizures (1 or more)†	NR	Yes	Difference in crash rate	Yes
Hansotia et al.(88)	1991	Case-control (retrospective)	241 individuals with epilepsy compared with 30,420 individuals without epilepsy	Individuals with a primary or secondary ICD-9-CM diagnosis of epilepsy (codes 345 to 345.9)	Generalized: 82.8% Simple partial: 17.2% Complex partial: 27.7% Other: 0.8%	No	Difference in crash rate	No
Popkin and Waller(89)	1989	Case-control (retrospective)	112 individuals with epilepsy compared with an unknown number of individuals without epilepsy	NR. However, all individuals were receiving treatment for epilepsy from the North Carolina Division of Health Services	Focal motor or Jacksonian seizure: 3.6% Temporal or psychomotor seizure: 21.4% Generalized: 57.1% 0ther: 17.8%	No	Difference in crash rate	No
Davis et al(90)	1973	Case-control	77 individuals with epilepsy compared	NR	NR	No	Difference in	No

Reference	Year	Design (prospective or retrospective)	Comparison	Definition of epilepsy used	Subtype(s) of epilepsy or seizure	Driving exposure controlled for?	Primary outcome	Outcome self-reported?
		(retrospective)	with 1,651,245 individuals without epilepsy matched for age and sex				crash rate	
Crancer and McMurray(91)	1968	Case-control (retrospective)	1,169 individuals with epilepsy compared with	NR	NR	No	Difference in crash rate	No
Waller(92)	1965	Case-control (retrospective	580 individuals with epilepsy compared with	History of episodes of loss of consciousness or of conscious control because of an intracranial lesion other than a lesion of a cerebral blood vessel.	NR	Yes	Difference in crash rate	Yes

*Crash estimates calculated using a prevalence estimate for epilepsy of 5.1/1,000 from National Center for Health Statistics and Census data for adults 18 years and older

†Group contains additional individuals who do not meet the typical definition of epilepsy;

Sheth et al.(84) analyzed Multiple-Cause of Mortality data files for 1995–97 to determine the number of seizure-related and non-seizure related crash fatalities in the United States per year. These data files were compiled from U.S. death certificates provided by the National Center for Health Statistics (NCHS) division of the Centers for Disease Control and Prevention (CDC) and included demographics, geographic information, and classification codes (from the International Classification of Disease, Ninth Revision [ICD-9]) presenting the underlying cause of death as well as any other conditions listed on the death certificate as "other significant conditions."The maximum number of conditions allowed for these data files was 20. Mortality data were coded in two ways: the entity axis format and the record axis format. The entity axis format provided a separate code for each disease listed, and whether it was an underlying cause of death or a contributory condition. The record axis format used linkage rules to combine listings of related conditions on the death certificate. Sheth et al. used the entity axis to determine the number of driving crash fatalities in which epilepsy and seizures were listed as primary contributing causes.

Using this information, Sheth and colleagues determined the numbers of fatal driver crashes per year associated with seizures and compared this with the number of fatal driver crashes not associated with any medical conditions. The ICD-9 codes used to screen for these conditions were as follows: (810.0 to 829.9 fatal road traffic crashes) epilepsy (345.0 to 345.9), and convulsions (780.3). The investigators calculated seizure-specific crash rates by comparing the number of fatal crashes associated with seizures with the expected annual prevalence of the disorder, which was estimated to be 1,000,535 individuals for the population aged ≥ 18 years.

Vernon et al.(85) reported on a retrospective case-control study in which they compared crash rates experienced by drivers licensed with a medical condition with age, sex, and location matched controls. Medical conditions examined included the following:

1. Diabetes mellitus and other metabolic conditions
2. Cardiovascular conditions
3. Pulmonary conditions

4. Neurological conditions
5. Epilepsy and other episodic conditions
6. Learning/memory/communications
7. Psychiatric or emotional conditions
8. Alcohol and other drugs
9. Visual acuity
10. Musculoskeletal abnormalities/chronic medical debilities
11. Functional motor ability
12. Hearing

Separate comparisons were made for each medical condition and for drivers reporting medical conditions licensed with full driving privileges, and those with restricted driving privileges (e.g. restrictions related to speed, area and time of day). The study population consisted of all drivers licensed in the state of Utah who self-reported a medical condition on their driver license application over the 5-year period 1992-1996. Control drivers were individuals without a medical condition who were chosen from the entire population of drivers licensed in Utah for the same period. Information on driver license status, participation in the Utah medical conditions program, citations, involvement in crashes, and death certificate data were obtained from the relevant state agencies. Probabilistic linkage methodology was used to link the records in these disparate databases for eventual analysis. Rates of citation, crashes and at-fault crashes, expressed as events per 10,000 license days, were calculated separately for program drivers and their corresponding control groups for each medical condition category and restriction status. These data were used to determine an estimate of relative risk (RR) and 95% confidence intervals.

Lings et al.(86) compared the crash rates per 1,000 person years for 159 drivers diagnosed with epilepsy (ICD–8) with 559 controls, individually matched for age, gender, place of residence, and exposure period. Exposure period was defined as the period of time following the diagnosis of epilepsy that each included individual held a driving license. This should not be confused with the typical measures of exposure used in crash risk studies (miles driven per year, the type of roads driven on, etc.) Lings et al. argued that this method was selected because the question of mileage is complex, with individuals with epilepsy potentially driving less than healthy drivers because of self-regulation or as a consequence of decreased employment activity. This self-regulation may thereby produce fewer crashes than others even if their mileage crash risk were great. The primary outcome of interest in the study of Lings et al.(86) was treatment at an emergency room following a motor vehicle crash as a car driver. Thus, their study does not take into account minor crashes or crashes that involve only material damage.

Taylor et al.(87) attempted to estimate the risks of motor vehicle crashes over a three-year period among drivers with a history of single seizures or epilepsy and compare them with the risks in a cohort of drivers from the general population. Enrollees consisted of 16,958 drivers with a history of seizures (recurrent or single) and 8,888 non-epileptic drivers who all responded to a questionnaire. Drivers were asked to complete questions regarding demographics details, information about their driving history, and if they had been involved in a crash as a driver over the previous three years. Drivers with epilepsy were also asked to complete questions regarding

the history of their seizures, information about their prescribed medications, and whether their seizures had ever resulted in a crash.

Hansotia and Broste(88) assessed the effect of epilepsy and diabetes mellitus on motor vehicle crashes (for data pertaining to diabetes mellitus and crash risk see the previous FMCSA Evidence Report, "Diabetes Mellitus and CMV Driver Safety"). Specifically the authors studied the crash rate per 1,000 person-years of licensed driving (standardized for age) over a four-year period (1985–1988) among 30,420 drivers. Participants were drivers aged 16–90 who had been recruited from the city and surrounding areas of Marshfield, WI. The 434 drivers with epilepsy were identified through the use of computerized ICD-9-CM diagnostic codes for epilepsy (345 to 345.9). Controls were active drivers who had no diagnostic code of epilepsy. Like several of the studies described above, this study did not adjust for exposure (i.e. number of miles driven, etc.). The authors noted that participants with epilepsy had numerous other medical conditions including strokes, dementia, clinical depression and other psychiatric disorders, but did not provide the prevalence of these comorbid conditions. No attempt was made to control for the presence of these conditions or several other important related factors such as: years since disease onset; disease severity; or disease treatment type in this study.

Popkin and Waller(89) examined the driving records of 112 drivers who utilized any one of six North Carolina Division of Health Services' clinics for the treatment of epilepsy during 1981–1982. Of those undergoing treatment at the clinics, 29 (26 percent) were known to the DMV to have epilepsy. Crash data from these 112 drivers was obtained from records held by the DMV and a crash incidence rate was determined. This crash rate was then compared with the expected crash rate for a population of individuals of selected from a "general population." The study investigators provide no details of this control group and it is unclear whether any attempt was made to match individuals with controls across any of the parameters normally considered to be important (age, sex, driving exposure, etc.). It seems that the control group was created as part of a previous study. However, we have been unable to obtain a copy of the article cited by Popkin and Waller that they report describes the creation and characteristics of this control group.

Davis et al.(90) examined the driving records of all individuals with medically restricted license who were granted drivers licenses after being reviewed by the Oklahoma Medical Advisory Committee (OMAC) in 1969. The authors recorded the number of crashes and moving violations accumulated during 1970 and compared these rates with those obtained from age and sex controls selected from Oklahoma's 1,651,245 licensed drivers. Accidents were considered to be single or multiple motor vehicle crashes in which the subject was the driver of a motor vehicle. All crashes in which the medically restricted person was a driver were included in the study. No attempt was made to control for exposure to risk in this study.

Crancer and McMurray(91) compared the driving records of Washington's medically restricted drivers with the driving records of all Washington motorists. Included among the motorists with medical restrictions were 1,169 drivers. Accident and violation rates for drivers with and without epilepsy license restrictions were compared. Comparisons were performed between gender and age groups. The record of each driver and the number of accidents accumulated during the period from Jan. 1961 to Oct. 1, 1967 was determined. Problems associated with the design of this study include the fact that an unknown number of drivers may not report medical conditions that will lead to medical restrictions being imposed and that exposure to risk was not controlled for.

Waller(92) assessed the driving records of 447 individuals with epilepsy who were known to the California Department of Motor Vehicles. Waller defined epilepsy as being a history of episodes of loss of consciousness or of conscious control because of an intracranial lesion other than a lesion of a cerebral blood vessel. For both samples, relevant information was obtained, through direct interviews or written questionnaires, regarding age, sex, marital status, occupation, and number of miles driven annually. An important limitations associated with this study is the fact that the sample of individuals with epilepsy was comprised only of those individuals known to the California Department of Motor Vehicles. It would be naive to assume that this sample represents a true cross-section of individuals who are driving with epilepsy because many individuals may not report their condition to the authorities.

Quality of Evidence Base

Our assessment of the quality of the studies that comprise the evidence base for Key Question 1 is summarized in Table 20. Our analysis found that the quality of all of the included studies varied from moderate to low.

Table 20. Quality of the studies that Assess Key Question 1

Reference	Year	Quality Scale Used	Quality Score	Quality
Sheth et al.(84)	2004	Revised Newcastle-Ottawa Scale	5.4	Low
Vernon et al.(85)	2002	Revised Newcastle-Ottawa Scale	9.2	Moderate
Lings(86)	2001	Revised Newcastle-Ottawa Scale	6.9	Low
Taylor et al.(87)	1996	Revised Newcastle-Ottawa Scale	5.2	Low
Hansotia et al.(88)	1991	Revised Newcastle-Ottawa Scale	5.4	Low
Popkin and Waller*(89)	1989	Revised Newcastle-Ottawa Scale	3.8	Extremely Low
Davis et al.(90)	1973	Revised Newcastle-Ottawa Scale	6.5	Low
Crancer and McMurray(91)	1968	Revised Newcastle-Ottawa Scale	6.2	Low
Waller(92)	1965	Revised Newcastle-Ottawa Scale	7.7	Low

*Excluded from further consideration (see text)

One of the included studies, Popkin and Waller, was found to be particularly poorly described. As a consequence, assessment of its quality using the Newcastle-Ottawa Scale concluded that the study was of extremely low quality. Consequently, this study was excluded from further consideration in the present evidence report.

The quality of the remaining eight studies ranged from moderate to low. This is consistent with the fact that all of the included studies utilized a case-control study design. By definition such a study design is always retrospective. Individuals with a specific disorder (cases), in this case epilepsy, are identified and information about the number of crashes experienced over some predefined period in the past is obtained. A group of individuals matched for several variables

(controls) is then identified and crash rates compared. Other important factors that potentially diminish the robustness of the findings of the case controls included in the present evidence base include the following:

- *Selection bias* – although cases and controls are usually matched for several variables (age, sex, etc.), comparability of the individuals in the two groups cannot be guaranteed. In the present study several important variables were not matched. For example, of the eight studies included in the evidence base for Key Question 1, only two studies attempted to match cases and controls for the annual mileage driven.(92,93) Therefore, one cannot be sure that differences in crash rate experienced by cases and controls were the consequence of the difference in disease state; they may simply be the result of a systematic difference in exposure to risk (more miles driven per year, the greater the exposure to risk).
- *Misclassification bias* – the results from many of the earlier included studies tended to be based on crash data retrospectively obtained from official government records while those from later years tend to be based on data obtained from self-reports. Both these methods of data collection subject a study to the potential for misclassification bias (individuals with a disorder being misclassified as not having the disorder or individuals who have crashed being classified as not having crashed). Data collected from government records will not necessarily provide reliable information on individual health status. This is because in many cases, individuals must report their health status to the authorities. It is known that many individuals with health disorders that will lead to restrictions on their driving license will not notify the authorities of their condition. Likewise, data collected from self reports relies on the honesty of individuals. In this case, individuals may be reluctant to provide accurate information on their health state and their driving record. Even assuming that all individuals are honest, the accuracy of these data must also be viewed cautiously because they rely on recollections of an individual which may not be accurate (sometimes called, "hindsight bias").

Generalizability of Evidence Base to Target Population

The purpose of this subsection is to provide details of the extent to which the individuals enrolled in the studies that address Key Question 1 are similar to CMV drivers in the United States. Important characteristics of the individuals included in the studies that address Key Question 1 are presented in Table 21. The generalizability of the findings of the included studies to CMV drivers is unclear. Not surprisingly, none of the included studies examined crash risk among individuals who held a current commercial driver's license. Exposure to risk is far lower among non-commercial vehicle drivers. This limits the value of the available data. Also, women tend to be overrepresented in studies of crash risk among drivers with private motor vehicle driver licenses and comorbidities tend to be underrepresented.

Table 21. Generalizability of Studies that Address Key Question 1

Reference	Year	(number of individuals with epilepsy included (n=)	Duration of epilepsy	% Male	% CMV drivers	Mean age (SD) in yrs	Driving exposure	% with medically restricted licenses?	Generalizability to target population
Sheth et al.(84)	2004	1,000,535*	NR	NR	NR	NR	NR	NR	Unclear
Vernon et al.(85)	2002	2,739	NR	NR	NR	NR	NR	Two groups: restricted and unrestricted	Unclear
Lings(86)	2001	159	NR	54.7	0.0	Males mdn: 38.8 Females mdn: 35.9	NR	0%	Unclear
Taylor et al.(87)	1996	16,958	NR	54.0	NR	Mdn: 38	Mdn: 6,000 miles per year	100%	Unclear
Hansotia et al.(88)	1991	241	NR	57.7	0.0	43.4	NR	NR	Unclear
Davis et al(90)	1973	77	NR	69.8	NR	NR	NR	100%	Unclear
Crancer and McMurray(91)	1968	1,169	NR	NR	NR	NR	NR	100%	Unclear
Waller(92)	1965	447	NR	73.8	NR	Males: 36.7 Females: 39.8	Males: 8,700 miles per year Females: 5,400 miles per year	100%	Unclear

*Number of individuals that comprise the denominator in risk calculations was estimated for the entire U.S. population (see text)

Findings

The findings of each of the eight studies (Median Quality Score = 6.4: Low) that address Key Question 1 are presented in detail in Appendix G. All eight presented data on the ratio of crashes experienced by a group of individuals with epilepsy compared with a group of individuals who did not have the disorder. Relevant data extracted from these studies are presented in Table 22 and graphically in Figure 5.

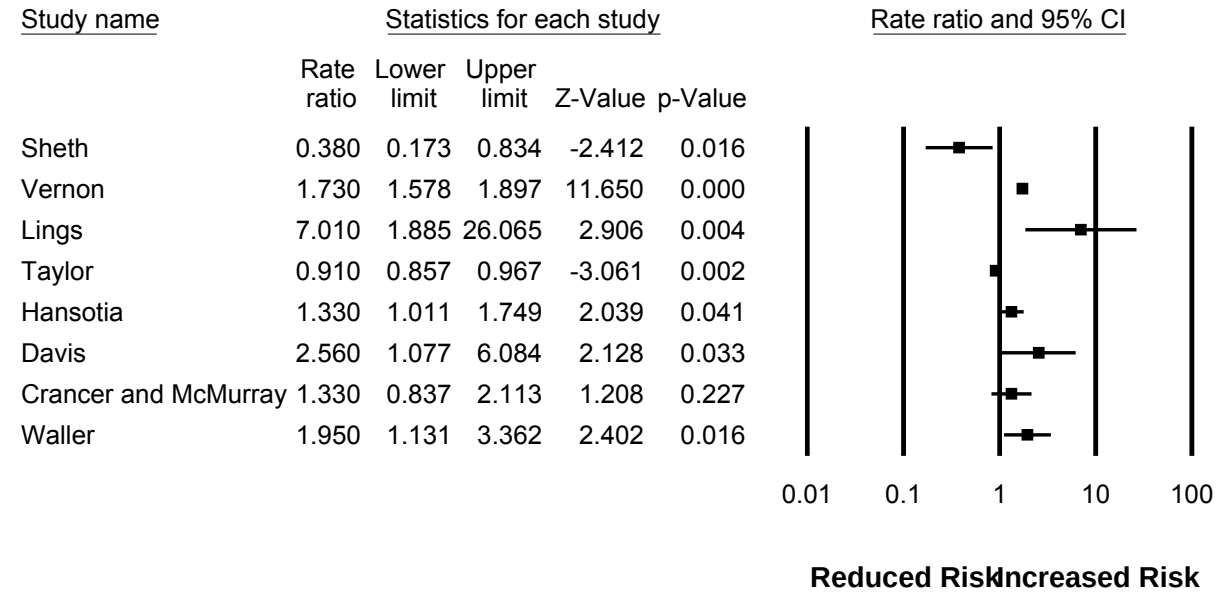
Table 22. Crash Risk in Drivers with Epilepsy compared to Drivers without Epilepsy

Reference	Year	Crash Rate Data					Bottom Line
		Group	Reported Crash Rate	Factors controlled for?	Crash Rate Ratio* (95% CI)	*P*=	Evidence of increased Crash Risk?
Sheth et al.(84)	2004	Cases	8.6 fatal crashes per 100,000 individuals per year	None	0.38 (0.17 to 0.83)	*0.016*	No
		Controls	22.4 fatal crashes per 100,000 individuals per year				
Vernon et al.(85)	2002	Cases	2.69 crashes per 10,000 license days – non-restricted group	Age, sex, place of residence	1.73 (1.58 to 1.90)	*<0.001*	Yes

Reference	Year	Crash Rate Data					Bottom Line
		Group	Reported Crash Rate	Factors controlled for?	Crash Rate Ratio* (95% CI)	*P*=	Evidence of increased Crash Risk?
		Controls	1.55 crashes per 10,000 license days – non-restricted group				
		Cases	2.67 crashes per 10,000 license days – restricted group	Age, sex, place of residence	1.47 (1.06 to 2.03)	*<0.001*	Yes
		Controls	1.81 crashes per 10,000 license days – restricted group				
Lings(86)	2001	Cases	9.4 crashes per 1,000 person years	Age, sex, place of residence, exposure period	7.01 (2.18 to 26.13)	*0.004*	Yes
		Controls	1.34 crashes per 1,000 person years				
Taylor et al.(87)	1996	Cases	3614 crashes among 16,958 individuals over 3 years	Age, sex, driving experience, mileage	0.91 (0.86 to 0.97)	*0.002*	No
		Controls	2068 crashers among 8888 individuals over 3 years				
Hansotia et al.(88)	1991	Cases	0.0685 crashes per person-year	Age	1.33 (1.00 to 1.73)	*0.041*	Yes
		Controls	0.0515 crashes per person-year				
Davis et al(90)	1973	Cases	18.2 crashes per 100 drivers per year	None	2.56 (1.08 to 6.10)	*0.033*	Yes
		Controls	7.1 crashes per 100 drivers per year				
Crancer and McMurray(91)	1968	Cases	41.44 crashes per 100 drivers per 5.75 years	Age	1.33 (0.84 to 2.12)	*0.227*	No
		Controls	31.06 crashes per 100 drivers per 5.75 years				
Waller(92)	1965	Cases	16.0 crashes per 1,000,000 miles	Age, mileage	1.95 (1.12 to 3.33)	*0.016*	Yes
		Controls	8.2 crashes per 1,000,000 miles				

*Calculated by ECRI. Effect size estimates >1.0 indicate that individuals with seizure disorders are at increased risk for a motor vehicle accident when compared to individuals without the disorder

Figure 5. Forest Plot of Data Presented in Table 22



It is clear from Table 22 and Figure 5 that the findings of the eight included studies are inconsistent. Five included studies found an increased risk associated with epilepsy (Vernon, Lings, Hansotia, Davies, and Waller), one included study found no evidence of an increased crash risk (Crancer and Murray) and two included studies found that crash risk was reduced among individuals with epilepsy (Sheth, Taylor). A formal assessment of these data for quantitative consistency (homogeneity testing) found that the findings of the eight studies were not comparable ($Q=59.59$, $P<0.0001$; $I^2=88.25$). Consequently we were precluded from combining crash rate ratio data from these studies in a fixed-effects meta-analysis in order to obtain a single estimate of the crash risk associated with epilepsy.

In an attempt to explain the heterogeneity we performed a series of univariate meta-regression analyses, as the development of multivariate models was precluded by the small size of the evidence base. The covariates considered in these analyses, which were chosen *a priori*, and the findings of each regression analysis are presented in Table 23.

Table 23. Findings of Univariate Meta-regression Analyses (unrestricted maximum likelihood models)

Covariate	Coefficient	95% CI	P=	Coefficient significant?	Residual	Model	Total	Tau²
Study level covariates								
Fatal crashes only	-1.38	-2.36 to -0.39	0.00594	Yes	Q=9.77, P=0.13476	Q=7.56857, P=0.00594	Q=17.33675 **P=0.01535**	0.07169
Mileage matched?	-0.16	-0.39 to 0.62	0.69269	No	Q=11.58, P=0.07199	Q=0.15618, P=0.07199	Q=11.73725, P=0.10945	0.18097
Age matched?	0.48	-0.41 to 1.37	0.28943	No	Q=11.30792, P=0.07931	Q=1.12228, P=0.28943	Q=12.43020, P=0.08727	0.16068
Sex matched?	0.21	-0.55 to 0.98	0.58441	No	Q=10.52934, P=0.10406	Q=0.29916, P=589441	Q=10.82850, P=0.14628	0.21215

Covariate	Coefficient	95% CI	P=	Coefficient significant?	Residual	Model	Total	Tau^2
Exposure period matched?	0.10	-0.81 to 1.01	0.82969	No	Q=10.64708, P=0.09992	Q=0.04672, P=0.82969	Q=10.69335, P=0.15257	0.21730
Years since publication	0.01	-0.01 to 0.03	0.30453	No	Q=11.86094, P=0.06514	Q=1.05427, P=0.30453	Q=12.91520, P=0.07420	0.14799
Self-reported outcome?	-0.16	-0.92 to 0.62	0.69269	No	Q=11.58107, P=0.07199	Q=0.15618, P=0.69269	Q=11.73725, P=0.10954	0.18097
Study Quality	0.21	-0.34 to 0.75	0.45964	No	Q=10.34161, P=0.06611	Q=0.54678, P=0.45964	Q=10.88839, P=0.09189	0.05621
Patient level covariates								
Mean age	NC	NC	NC	NC	NC	NC	NC	NC
% male	NC	NC	NC	NC	NC	NC	NC	NC
% CMV drivers	NC	NC	NC	NC	NC	NC	NC	NC
Mean duration of epilepsy	NC	NC	NC	NC	NC	NC	NC	NC
% with medically restricted licenses	NC	NC	NC	NC	NC	NC	NC	NC
Mean # of AEDs	NC	NC	NC	NC	NC	NC	NC	NC
% with comorbid conditions	NC	NC	NC	NC	NC	NC	NC	NC

NC=not calculated because necessary data was not reported by all included studies

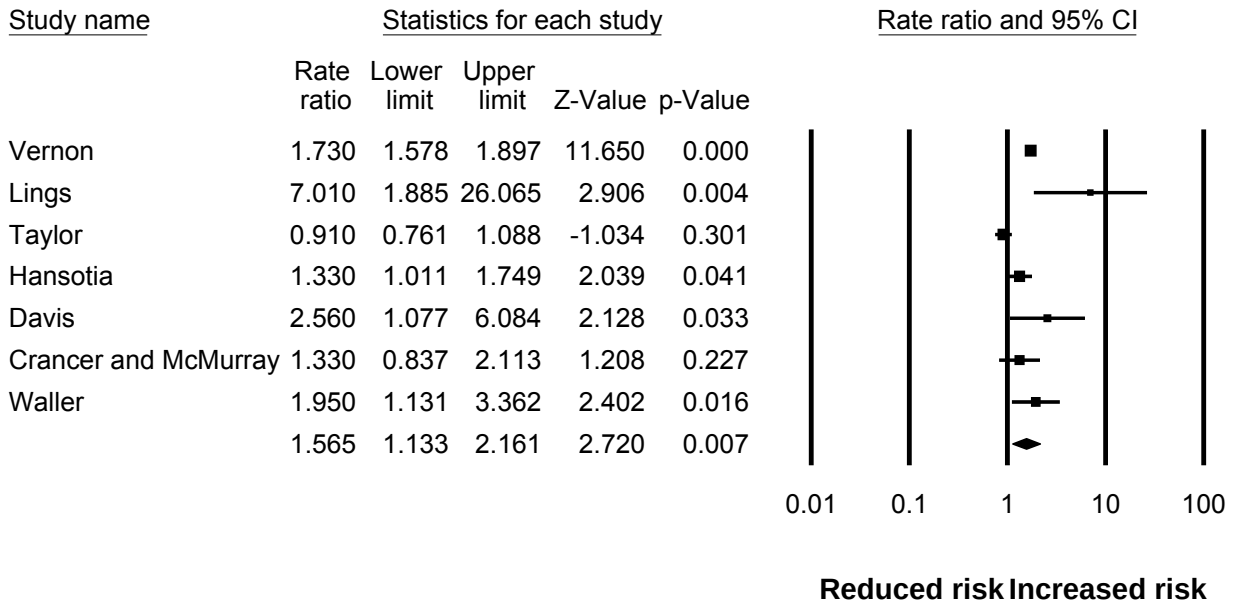
Our meta-regression analyses found that only one of the covariates examined was significantly correlated with outcome; this covariate being whether the study evaluated fatal crashes only. If the impact of the study of Sheth et al. (the only study to have evaluated the difference in fatal crash rates among individuals with epilepsy and a comparison of individuals without epilepsy) on the estimated crash rate ratio is controlled for, one finds that the estimated crash risk ratio for an individual with epilepsy is estimated to be 1.51 (95 percent CI: 1.40 to 1.63).

Unfortunately, even though our analyses found that inclusion of the study of Sheth et al. in the evidence base had a significant impact on outcome, adjusting for its presence did not eliminate heterogeneity (adjusted Q=47.832, P<0.0001; adjusted I^2=87.456). This unexplained quantitative inconsistency in these data precludes one from determining a single estimate of the increased risk for a crash for an individual with epilepsy when compared to comparable individuals who do not have the disorder.

Pooling of data from the included studies (with Sheth et al. excluded[9]) using a random effects meta-analysis found that on average, individuals with epilepsy are significantly more likely (somewhere between 13 percent and 116 percent more likely) to experience a crash than comparable individuals who do not have the disorder (Figure 6). This finding is robust (see Appendix H).

[9] If data from Sheth et al. is included in analysis an increased crash risk is still observed (risk for a crash is between 0% and 95%).

Figure 6. Random Effects Meta-Analysis of Crash Rate Risk Data



Additional Information on Risk Factors for Crash among Individuals with Epilepsy

Krauss et al.(94) conducted a retrospective case-control study aimed at identifying risk factors for a motor vehicle crash due to seizures. Specifically, the authors compared 50 drivers with epilepsy who had a motor vehicle crash which could be attributed to a seizure (cases) with 50 drivers with epilepsy who had not had a motor vehicle crash which could be attributed to a seizure (controls). Case and control participants were recruited from the same epilepsy clinic and were matched for gender and age. Participants were excluded if their epilepsy was in remission due to AED treatment during the study year or if they had had epilepsy surgery during the study year. Participants were also excluded if they crashed during their first seizure because the authors would be unable to collect clinical information regarding AED compliance, seizure-free intervals, and number of seizure related crashes. The following clinical characteristics and driving histories of case and control participants were collected using a self-report questionnaire: demographic data; seizure information; treatment factors; driving history; crash variables; and regulatory factors.

Krauss and colleagues reported that the following factors were most strongly associated with *reduced* odds for crashing:

- Long seizure intervals (12 months or longer and 6 months or longer) appeared to be associated with a reduced risk for a seizure-related crash (OR: 0.075; CI 0.012 – 0.47; OR: 0.147, CI 0.031-0.691, respectively).
- Drivers with reliable auras (i.e., where drivers reported always having auras at the start of seizures) were found to be a reduced risk for a seizure related crash (OR: 0.077). The study investigators noted, however, that some drivers who experienced auras did crash. This appeared to be the consequence of the fact that the individual concerned either continued to drive despite the aura or were unable to stop driving before the seizure progressed because the aura was too brief in duration.

- Drivers who switched or reduced the dose of their AEDs were found to be at lower risk for crash (OR: 0.111). This is surprising because the risk for a seizure is thought to increase during drug switching or tapering. Krauss suggested that this finding may be the consequence of the drivers having fewer seizures when their AEDs were consolidated (reduced from several to one) or switched.
- Drivers who had few crashes in the past were found to be at a significantly reduced risk for experiencing a seizure-related crash (OR: 0.465).

Other findings noted by Krauss et al. were that 25 percent of drivers had more than one seizure-related crash, 20 percent had just missed an AED dose prior to their crash, 4.6 times as many men experienced seizure related crashes compared to women, and that 54 percent of drivers who crashed were driving illegally with seizure free intervals shorter than legally permitted. The authors concluded that seizure free intervals, the presence of reliable auras, AED therapy modifications, and a history of non-seizure induced crashes should be considered when advising individuals with epilepsy about driving.

Taylor et al.(87) found no evidence supporting the contention that taking AEDs increased the risks of any form of crash in a population of drivers with a history of epilepsy (OR: 0.97, CI 0.87-1.07). Taylor et al. also reported that the absence of seizures over a three year period appeared to halve the risk of serious injury or fatal crashes (OR: 0.56, CI 0.32-0.96). It was also concluded that the crash rates for individuals with epilepsy are no greater than the general population after adjusting for age, gender, driving experience and mileage. An important limitation of this study involved the combination of participants who had experienced a single seizure with those who had a history or diagnosis of epilepsy. As noted previously, epilepsy is only diagnosed after two or more seizures; therefore the non-significant findings of the study may be attributable to the fact that some participants in the epilepsy group would not actually have a diagnosis of epilepsy. In addition, although the authors made adjustments for important factors such as age, gender and driver exposure, they did not specify whether participants in either group were screened for other comorbid medical conditions.

Gastaut and Zifkin(95) attempted to determine the risk of motor vehicle crashes posed by various seizure types when they occur during driving. Of 400 drivers with epilepsy approached by the study investigators, 133 admitted to having had one or more seizures at the wheel. Of these, 82 were able to describe or have a witness describe the seizure in enough detail for it to be classified. These 82 drivers experienced a total of 109 identified seizures at the wheel, with 60 of these seizures leading to a crash. The most common seizure types to be associated with a crash were complex partial seizures without aura, secondarily generalized seizures, and generalized tonic clonic seizures. The seizure types least likely to be associated with a crash were simple partial seizures, complex partial seizures with aura, absence seizures, and myoclonic seizures.

Section Summary

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 sufficient to explain a sufficiently large degree of heterogeneity for us to present a single estimate of the crash rate ratio. Pooling 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?

Introduction

Standard treatments for epilepsy include the use of antiepileptic medications (AEDs) and surgery. Both treatment options aim at suppressing seizures and/or epileptiform activity and reducing the severity of the seizures.(96) The National Institute of Neurological Disorders and Stroke (NINDS) have estimated that approximately 80 percent of individuals diagnosed with epilepsy will achieve "successful" seizure control with AEDs or surgery.(24)

AED Treatment for Epilepsy

Antiepileptic drugs work primarily by altering ion channel and neurotransmitter system functions. AEDs cannot be considered as providing a 'cure' for epilepsy; rather, they serve to maximize seizure control by either enhancing inhibitory processes or opposing excitatory processes in the brain.(16,97) Ideally, an individual who has been newly diagnosed with epilepsy will begin treatment with a single AED (monotherapy). If seizures continue, new seizures develop or intolerable adverse events occur, monotherapy with a different AED will be tried. If this is unsuccessful and seizures continue, addition of another AED (duotherapy) or several AEDs (polytherapy) is usually considered.

Effectiveness of AEDs

There are a wide variety of pharmacotherapeutics available for the treatment of epilepsy (see Table 7 in the *Background* section). The 'traditional' antiepileptic drugs (those developed before 1993) – phenytoin, phenobarbital, primidone, carbamazepine, and valproate – used to treat seizure disorders have the benefit of proven efficacy, lower cost, and familiarity among physicians.(20,98) However, these antiepileptic drugs are also associated with intolerable adverse effects such as transient leukopenia (carbamazepine), osteomalacia (phenytoin) weight

gain (valproate), and a potential for drug interactions, and individuals using these medications may be more prone to experiencing recurrent seizures.(20,99) The 'newer' antiepileptic drugs (those developed after 1993) – felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, and zonisamide – have the benefit of fewer drug interactions than the traditional AEDs, a broader spectrum treatment activity, and fewer adverse events.(20)

The aim of AED therapy is the rapid control of seizure activity with a minimum of adverse effects in order to maintain a normal lifestyle.(100) Ideally, seizure control is provided through monotherapy (the use of a single AED), to reduce the likelihood of drug interactions and adverse effects: with this understanding in mind, nearly 70 percent of individuals receiving AEDs are managed via monotherapy.(101) In newly diagnosed individuals who began AED therapy, Kwan and Brodie found that approximately 64 percent entered terminal remission of at least one year.(97) A review of adult epilepsy by Duncan et al. found that 60 percent to 70 percent of all individuals achieved effective seizure control while using AED therapy: this figure closely matches those found in a review by Sander, which stated that one year remission rates varied between 58 percent and 95 percent, with most studies reporting rates between 65 percent and 80 percent.(96,102) Similar figures may be found in single studies by Cockerell et al. (54 percent remission within one year of AED treatment inception), and Annegers (probability of 5 seizure-free years remission within 10 years of AED inception, 65 percent).(103,104) Looking at these studies and reviews overall, seizure-free rates for individuals using AED therapy fell between 58 percent and 95 percent, with most falling between 65 percent and 75 percent. Ultimately, methodological issues such as mixing of populations with different seizure etiologies and seizure types make determining the remission rates associated with AED related treatment difficult to determine, as the most accurate remission rates would be most likely to be produced by studies of individuals with the same type of epilepsy, or the same etiology.

Seizure Recurrence Among Individuals on AEDs

Some individuals who achieve remission from seizures while on AEDs will experience seizure recurrence. Several factors have been identified which are predictive of seizure recurrence among individuals who achieve seizure freedom while on AEDs (Table 24 and Table 25). The most important of these factors appear to be the number of years of remission (the longer the seizure-free period, the lower the risk for seizure recurrence type of seizure), the number of antiepileptic drugs utilized (monotherapy, duotherapy, or polytherapy with the latter two being associated with a greater risk for recurrence), the response to AED therapy (did the individual had a positive response to the first AED of choice, or were other AED therapies attempted after failure of the initial AED to control seizures), seizure type (juvenile myoclonic epilepsy, partial seizures, including complex and those with secondary generalization), seizure frequency prior to beginning AED treatment (higher seizure frequencies are associated with an increased risk for seizure recurrence), and electroencephalogram (EEG) abnormalities (a lack of abnormalities appears to be associated with an decreased risk for seizure recurrence) (Figure 7).

Table 24. Factors Associated with Seizure Recurrence

Reference	Year	Study Size and Followup	Study Design	Prospective or Retrospective	Population Characteristics	Prognostic Factor Examined	Results
Aktekin et al.(105)	2006	A total of 54 patients were enrolled in the AED discontinuation process. There were 4 dropouts. One patient died due to a heart attack.	Cohort study	Prospective	**Seizure-free group** Age: 38.43 ± 17.35 Gender: 11 (M), 10 (F) Age at onset: 26 ± 17.9 Duration of active disease (months): 104.67 ± 63.85 **Relapsed group** Age: 39.39 ± 13.68 Gender: 11 (M), 17 (F) Age at onset: 17.4 ± 13.3 Duration of active disease (months): 237.56 ± 130.94	AED withdrawal Age at onset of epilepsy Duration of active disease Age Gender History of perinatal anoxia or febrile seizures Family history of epilepsy Mental retardation History of status epilepticus Number and type of AEDs	Affecting Risk of Relapse: • Age at onset of epilepsy • Duration of active disease Not Related to Risk of Relapse • Age • Gender • History of perinatal anoxia or febrile seizures • Family history of epilepsy • Mental retardation • History of status epilepticus • Number and type of AEDs
Sillanpää and Schmidt(106)	2006	148 children with epilepsy who were followed for more than 9 years from the onset of their epilepsy (mean ± SD = 37 ± 7.1 years, median = 40 years, range = 11 – 42 years)	Cohort study	Prospective	Not Reported	AED withdrawal	AED withdrawal : • Results in relapse in 30% of patients. No evidence that AED withdrawal is responsible for the poor prognosis for treatment of seizure recurrence.
Kalita et al.(107)	2005	120 patients with epilepsy	Cohort study	Prospective	Gender: 86 (M), 34 (F) Mean age: 26.8 years (range, 13 – 71 years) Mean pretreatment seizure frequency: 6.2 (range, 2 – 40) Mean duration of epilepsy: 2.9 years (range, 0.3 – 9 years) 62 patients had partial seizure, 47 generalized and 11 had multiple types of seizures.	Number of AEDs Seizure type Seizure frequency Neurological deficit Electroencephalogram (EEG)	Seizure Remission: • A majority of individuals with epilepsy have seizure remission on monotherapy • Some on duotherapy • No seizure remission can be achieved on adding more than 2 drugs. One year seizure remission • Significantly related to type and frequency of seizure • Presence or absence of neurological or EEG abnormalities. Poor Remission: • Cryptogenic epilepsy • More than one seizure per month • Neurological deficit

Reference	Year	Study Size and Followup	Study Design	Prospective or Retrospective	Population Characteristics	Prognostic Factor Examined	Results
							• EEG abnormalities
Cardoso et al.(108)	2003	Ninety-four patients were followed up: 45 were assigned to complete (Group 1) AED withdrawal and 49 to partial (Group 2) AED withdrawal. The follow-up period was 24 months.	Randomized controlled trial	Prospective	Gender: 50 (M), 44 (F) Median age when withdrawal was initiated: 30.3 years (range, 15 – 76 years) Median age at epilepsy onset: 16.9 years (range, 0.1 – 62 years) Median active epileptic duration: 10.7 years (range, 0.1 – 40 years) Seizure control period before withdrawal: 64 patients (2 – 3 years), 17 patients (3 – 4 years), and 13 patients (≥ 4 years)	Low AED dose Gender Seizure type Total number of seizures Neurological examination CT scan Electroencephalogram (EEG) Age at epilepsy onset Active epilepsy duration Number of AEDs Maximal previous seizure frequency Previous AED withdrawal Age at AED withdrawal Etiology Family history of seizures Years of seizure control Type of AED	Leaving seizure free patients on low AED dose did not reduce the risk for seizure recurrence. Correlation with post-AED withdrawal risk of seizure recurrence • Number of seizures prior to control • >10 seizures before achieving control presented a risk 2.72 times greater than those who presented up to 10 seizures.
Specchio et al.(109)	2002	330 epilepsy patients who were seizure free for at least 2 years while on stable monotherapy. 225 patients were withdrawn from AEDs and 105 continued AED treatment.	Cohort study	Prospective	**Treatment withdrawn** Age (y): < 15, n = 38 15 – 34, n = 158 35 – 54, n = 22 > 54, n = 7 Gender: 103 (M), 122 (F) **Treatment continued** Age (y): < 15, n = 4 15 – 34, n = 77 35 – 54, n = 18 > 54, n = 6 Gender: 42 (M), 63 (F)	Age Gender Education AED withdrawal Duration of epilepsy Number of years of remission Psychiatric disorder Seizure type	Risk of Relapse • Withdrawal of AED: 2.9 times that of patients continuing treatment. • Factors affecting the risk of relapse duration of active disease • Number of years of remission while on treatment. • Abnormal psychiatric findings. The risk of relapse also varied markedly according to the epilepsy syndrome.
Kwan and Brodie(101)	2000	The study included 525 consecutive unselected children, adolescents, and adults in whom epilepsy was diagnosed and	Cohort study	Prospective	Gender: 259 (M), 266 (F) 470 patients had never received antiepileptic-drug therapy Median duration of follow-up: 5 years (range, 2 – 16)	Number of seizures before inception of AED therapy Known or probable cerebral structural abnormality Response to AED therapy	Refractory Epilepsy • Individuals who experience multiple seizures before inception of AED therapy individuals who have an inadequate response to

Reference	Year	Study Size and Followup	Study Design	Prospective or Retrospective	Population Characteristics	Prognostic Factor Examined	Results
		antiepileptic-drug therapy was begun.			Median age at referral: 29 years (range, 9 – 93) Median age at epilepsy onset: 26 years (range, <1 – 92)	(monotherapy vs. polytherapy) Response to AED therapy (early or late) Response to first AED	initial treatment with AEDs Early response to AED therapy confers a favorable prognosis Good response to first AED administered confers a favorable prognosis
Lossius et al.(110)	1999	669 patients with confirmed epilepsy were divided into 2 groups: (1) no seizures during the previous year (n = 485) and (2) seizures during the previous year (n = 184)	Cohort study	Prospective	Gender: 338 (M), 331 (F) Age; mean (SD): 44 (12) Seizure free (%): 484 (73)	Neurologic deficit Number of AEDs used CT-scan findings Electroencephalogram (EEG) Etiology Gender Age Comorbidity	Predictors for recurrence of seizures (univariate) • Age above 50 years • Known etiology • Use of two or more AEDs. Predictors for recurrence of seizures (multivariate) • Age > 50 years • Polytherapy
Chadwick et al.(111)	1996	409 patients who experienced a seizure recurrence following randomization to either: slow AED discontinuation (n = 245) or continued AED treatment (n = 164)	Randomized controlled trial	Prospective	Not Reported	Psychiatric disorder Neonatal seizures Febrile seizures Less than 1 AED at randomization Seizures after initiation of AED treatment Total seizure-free period Partial seizures at recurrence Myoclonic seizures at recurrence AEDs ever reduced Policy at recurrence	Long Term Remission The longer the total seizure-free period before a seizure Risk of Recurrence • Experiencing seizures while receiving AED treatment • Experiencing partial seizures at recurrence Little difference between individuals who: • Continued with AED use • Were still receiving therapy at recurrence, and had no change in treatment post-recurrence • Individuals who were randomized to slow AED withdrawal, were not receiving therapy at recurrence, and who subsequently restarted treatment Multiple seizures during followup • 20% of individuals randomized to continue AED treatment • 32% of individuals randomized to slow AED withdrawal
Quality Standards Subcommittee of the American Academy	1996	17 total studies (N = 2,957) 8 studies on children (N =	Systematic review	Studies on children 5 prospective, 3	Not Reported	Gender Age of onset	Predictors of remission • Longer duration of seizure control

Reference	Year	Study Size and Followup	Study Design	Prospective or Retrospective	Population Characteristics	Prognostic Factor Examined	Results
of Neurology(112)		1,377) 9 studies on adults (N = 1,580)		retrospective Studies on adults 1 randomized controlled trial, 3 prospective, 5 retrospective		Seizure type Etiology Neurologic examination/I.Q. Duration of seizure freedom on AEDs Treatment regimen Age at relapse Electroencephalogram (EEG)	with AEDs, the better the prognosis. Evidence presented in the 17 studies suggests that although their recurrence risk rates differ, both children and adults patients meeting the following profile have the greatest chance for successful drug withdrawal: • Seizure-free 2 to 5 years on AEDs (mean 3.5 years); • Single type of partial or generalized seizure; • Normal neurological examination and normal I.Q.; • EEG normalized with treatment.
Cockerell et al.(103)	1995	Remission was analyzed in those patients who were classified after 6 months as having definite epilepsy (n = 564) or possible epilepsy (n = 228).	Cohort study	Prospective	Not Reported	Age Gender Seizure type Age at onset of seizures	There was no discernible effect of seizure type or age at onset of seizures on remission
Nakazawa et al.(113)	1995	43 patients with epilepsy in whom AEDs were withdrawn completely	Cohort study	Prospective	Mean age at seizure onset: 16.9 ± 14.8 (range, 1.5 – 63.7) years Mean age at initial treatment: 18.2 ± 14.8 (range, 2.4 – 63.7) years Mean age at last seizure: 19.9 ± 14.9 (range, 2.5 – 67.6) years Mean age at disappearance of epileptic discharge: 23.7 ± 14.8 (range, 8.5 – 68.5) years Mean age at commencement of dose reduction: 25.8 ± 15.5 (range, 9.0 – 77.0) years Mean age at AED withdrawal: 28.1 ± 15.3 (range, 9.8 – 78.3) years	Total number of seizures Frequency of seizures Psychiatric disorder Seizure type Duration of epilepsy Electroencephalogram (EEG)	Not a risk factor for recurrence • The severity of epilepsy judged by the total number and frequency of seizures • Presence of neuropsychiatric complications • Combination of different types of seizures • Duration of epilepsy from the seizure onset to the last seizure Normal EEG was considered to be an important prerequisite for a good prognosis.
Berg and Shinnar(114)	1994	25 total studies (N = 5,354) Childhood- vs. adolescent-onset epilepsy: 17 studies (N = 4,383) Childhood- vs. adult-onset epilepsy: 7 studies (N = 1,911)	Meta-analysis	Not Applicable	Not Reported	Age at onset of epilepsy Underlying etiology Electroencephalogram (EEG)	Risk of post-AED withdrawal relapse was higher when (compared to childhood-onset epilepsy) • Adolescent-onset epilepsy • Adult-onset epilepsy Associated with risk of relapse

Reference	Year	Study Size and Followup	Study Design	Prospective or Retrospective	Population Characteristics	Prognostic Factor Examined	Results
		Remote symptomatic vs. idiopathic (nonsymptomatic) seizures: 14 studies (N = 3,395) Electroencephalogram: 15 studies (N = 3,849)					• Remote symptomatic seizures • Abnormal EEG
Mukasa et al.(115)	1994	36 patients with epilepsy who were withdrawn from AEDs	Cohort study	Prospective	Gender: 19 (M), 17 (F) Mean age at treatment termination: 17.7 (range, 2.6 – 50) years	Seizure frequency Neurological and mental complications Age at seizure onset Age at initial treatment Age at a new referral to clinic Age at last seizure Age at EEG normalization Age at start of AED reduction Age at AED termination Interval from the start of AED reduction to discontinuation of AEDs	Interval from the last seizure to the time of starting drug reduction shorter for the relapsed group than for non-relapsed group.
MRC Antiepileptic Drug Withdrawal Study Group(116)	1993	1,013 patients randomized to either continued use of AEDs (n = 510) or slow withdrawal (n = 503)	Randomized controlled trial	Prospective	**Continued use of AEDs** Gender: 49% (M), 51% (F) Median age at entry to trial: 26 (16, 39) years Median age at onset: 13 (6, 21) years Median duration of epilepsy: 5 (1.3, 11.7) years Median period seizure free: 3.2 (2.4, 5.8) years Median duration of AED treatment: 7.9 (3.5, 16.6) years **Slow withdrawal** Gender: 49% (M), 51% (F) Median age at entry to trial: 27 (17, 42) years Median age at onset: 14 (7, 24) years Median duration of epilepsy: 4.4 (0.8, 11.7) years	Gender Age Mental retardation Trauma Psychiatric disorder Family history of epilepsy Neonatal seizures Febrile seizures Age at first seizure Seizures only on awakening Seizures only while asleep Seizure type Absence of seizures Status Previous attempt to withdrawal from AED Number of AEDs Seizures after AED treatment Period free from seizures	Factors that increased the risk of seizures recurring included: • 16 years or older • Taking more than one AED • Experiencing seizures after starting AED treatment • History of primary or secondarily generalized tonic-clonic seizures • History of myoclonic seizures • Abnormal EEG. Decrease in seizure recurrence risk: • Increasing time without seizures.

Reference	Year	Study Size and Followup	Study Design	Prospective or Retrospective	Population Characteristics	Prognostic Factor Examined	Results
					Median period seizure free: 3.4 (2.3, 5.7) years Median duration of AED treatment: 7.1 (3.3, 15.4) years	Duration of epilepsy Duration of AED treatment Electroencephalogram (EEG)	
Tanaka et al.(117)	1992	334 patients with epilepsy who had received AED therapy for at least 8 years	Cohort study	Prospective	Gender: 164 (M), 170 (F) Mean age: 37.4 (range, 20 – 65) years Idiopathic (nonsymptomatic) generalized epilepsy (IGE) occurred in 65 patients, symptomatic generalized epilepsy (SGE) in 24, temporal lobe epilepsy (TLE) in 120, partial epilepsy other than the temporal lobe form (NTLE) in 99 and other epilepsies (UNC) in 26.	Gender Age Duration of epilepsy Duration of treatment Etiology Seizure type Seizure frequency Age at onset Type of epilepsy Number of AEDs History of febrile convulsion CT abnormality Electroencephalogram (EEG)	No significant differences in • Gender • Present age • Age at onset • Duration of epilepsy • Duration of treatment • Symptomatic etiology • History of febrile convulsion • Epilepsy classification • Type of seizure • Maximum seizure frequency • CT abnormality • Slowing of EEG background activity • EEG improvement during treatment. More patients with nonrecurring than recurring seizures received AED monotherapy.
MRC Antiepileptic Drug Withdrawal Study Group(118)	1991	1,013 patients randomized to either continued use of AEDs (n = 510) or slow withdrawal (n = 503)	Randomized controlled trial	Prospective	**Continued use of AEDs** Gender: 49% (M), 51% (F) Median age at entry to trial: 26 (16, 39) years Median age at onset: 13 (6, 21) years Median duration of epilepsy: 5 (1.3, 11.7) years Median period seizure free: 3.2 (2.4, 5.8) years Median duration of AED treatment: 7.9 (3.5, 16.6) years **Slow withdrawal** Gender: 49% (M), 51% (F) Median age at entry to trial: 27 (17, 42) years	Gender Age Mental retardation Trauma Psychiatric disorder Family history of epilepsy Neonatal seizures Febrile seizures Age at first seizure Seizures only on awakening Seizures only while asleep Seizure type Absence of seizures Previous attempt to withdrawal from AED	Factors influencing recurrence include: • Polytherapy at randomization • History of either primary or secondarily Generalized tonic-clonic seizures • Period free of seizures at randomization. Factors that might also be important • History of neonatal seizures, of myoclonic seizures, and of "never-generalized" partial seizures • Occurrence of seizures after initiation of AED treatment • Duration of AED treatment

Reference	Year	Study Size and Followup	Study Design	Prospective or Retrospective	Population Characteristics	Prognostic Factor Examined	Results
					Median age at onset: 14 (7, 24) years Median duration of epilepsy: 4.4 (0.8, 11.7) years Median period seizure free: 3.4 (2.3, 5.7) years Median duration of AED treatment: 7.1 (3.3, 15.4) years	Number of AEDs Seizures after AED treatment Period free from seizures Duration of epilepsy Duration of AED treatment Electroencephalogram (EEG)	
Callaghan et al.(119)	1988	The authors discontinued AED treatment in 92 patients who had been free of seizures during 2 years of treatment with a single drug. All the patients had epilepsy that had been previously been untreated, and had been randomly assigned to receive carbamazepine, phenytoin, or sodium valproate.	Randomized controlled trial	Prospective	Gender: 40 (M), 52 (F) Mean age: 24 years Mean duration of follow-up after withdrawal: 26 (range, 6 – 62) months	Gender Age Duration of epilepsy Duration of treatment Electroencephalogram (EEG) Seizure type AED treatment Seizure frequency	Significant factors for relapse: • Duration of treatment • Seizure type • Number of drugs required for seizure control • Number of seizures before the achievement of control • EEG classification
Beghi et al.(120)	1988	270 individuals with an average length of follow-up being 20.4 months (range: 2 – 40 months)	Cohort Study	Prospective	Gender: 160 (M), 143 (F) Mean age: 19 years (range: 2 – 81) Mean duration of follow-up: 20.4 months (range: 2 – 40 months)	Gender Age Number of seizures prior to treatment Type of seizures Number of seizures Duration of disease Risk factors (family history of epilepsy, neonatal convulsions, etc.) Etiologic factors Neurologic exam EEG epileptiform abnormal	Significant factors for relapse: • Number of seizures prior to treatment • Number of seizures
Annegers et al.(104)	1979	457 patients, of which 328 were followed at least 10 years and 141 at least 20 years	Cohort study	Prospective	Not Reported	Etiology of seizures Seizure type Age at diagnosis Gender	Prognosis for remission of epilepsy is poor in: • Patients with associated neurologic dysfunction identified from birth. Prognosis for remission of epilepsy is less favorable with: • Partial complex seizures • Adult-onset epilepsy

Reference	Year	Study Size and Followup	Study Design	Prospective or Retrospective	Population Characteristics	Prognostic Factor Examined	Results
							Eventual Remission Prospects better in: • Patients with idiopathic (nonsymptomatic) seizures • Survivors of postnatally acquired epilepsy Highest probability of remission among: • Individuals with generalized-onset seizures diagnosed before 10 years of age. There is little difference in prospect for remission between males and females. The likelihood of relapse increased with advance in age at diagnosis.

Table 25. Independent Risk Factors for Seizure Recurrence or Relapse Examined by Study

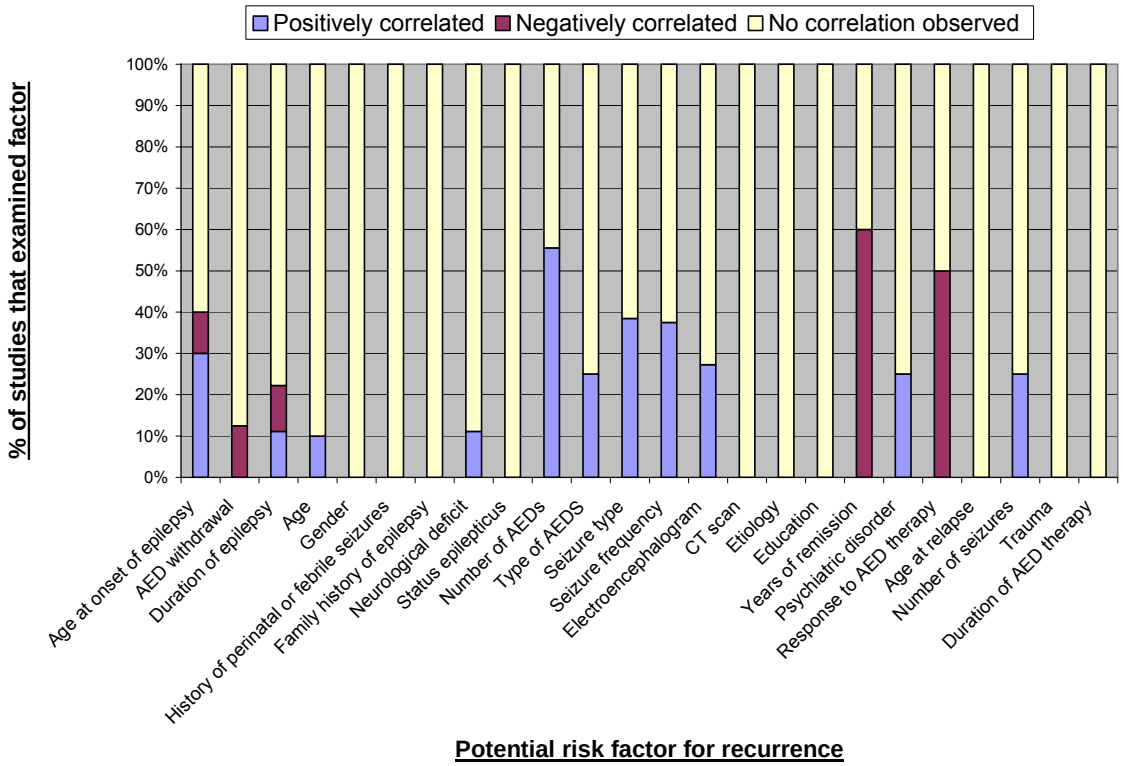
		Risk Factors																						
Reference	Year	Age at onset of epilepsy	AED withdrawal	Duration of epilepsy	Age	Gender	History of perinatal or febrile seizures	Family history of epilepsy	Neurological deficit	Status epilepticus	Number of AEDs	Type of AEDS	Seizure type	Seizure frequency	Electroencephalogram	CT scan	Etiology	Education	Years of remission	Psychiatric disorder	Response to AED therapy	Age at relapse	Number of seizures	Trauma	Duration of AED therapy
Aktekin et al.(105)	2006	√‡	√	√‡	√	√	√	√	√	√	√	√													
Sillanpää and Schmidt(106)	2006		√																						
Kalita et al.(107)	2005								√†		√†		√†	√	√†										
Cardoso et al.(108)	2003	√	√	√		√		√	√		√	√	√	√†	√	√	√								
Specchio et al.(109)	2002		√	√†	√	√							√					√	√‡	√†					
Kwan and Brodie(101)	2000								√					√†							√‡				
Lossius et al.(110)	1999				√†	√			√		√				√	√	√								

		Risk Factors																						
Reference	Year	Age at onset of epilepsy	AED withdrawal	Duration of epilepsy	Age	Gender	History of perinatal or febrile seizures	Family history of epilepsy	Neurological deficit	Status epilepticus	Number of AEDs	Type of AEDS	Seizure type	Seizure frequency	Electroencephalogram	CT scan	Etiology	Education	Years of remission	Psychiatric disorder	Response to AED therapy	Age at relapse	Number of seizures	Trauma	Duration of AED therapy
Chadwick et al.(111)	1996		√				√				√†		√	√					√	√					
Quality Standards Subcommittee of the American Academy of Neurology(112)	1996	√				√			√		√	√	√		√		√		√‡			√			
Cockerell et al.(103)	1995	√			√	√							√												
Nakazawa et al.(113)	1995			√									√	√	√						√		√		
Berg and Shinnar(114)	1994	√													√†		√								
Mukasa et al.(115)	1994	√	√‡		√				√					√								√			
MRC Antiepileptic Drug Withdrawal Study Group(116)	1993	√†	√	√	√	√	√	√	√		√†		√†		√				√‡	√			√	√	√
Tanaka et al.(117)	1992	√		√	√	√	√				√†		√	√	√	√	√								√
MRC Antiepileptic Drug Withdrawal Study Group(118)	1991	√	√	√	√	√	√	√	√		√†		√†		√				√	√			√	√	√
Callaghan et al.(119)	1988			√	√	√						√†	√†	√†	√†										√
Beghi et al.(120)	1988			√	√	√	√	√							√		√						√†		
Annegers et al.(104)	1979	√†				√							√†				√								
Total studies that evaluated relationship		10	8	9	10	12	6	5	9	1	9	4	13	8	11	3	7	1	5	4	2	2	4	2	4
Total +ve Correlations		3	0	1	1	0	0	0	1	0	5	1	5	3	3	0	0	0	0	1	0	0	1	0	0

		Risk Factors																							
		Age at onset of epilepsy	AED withdrawal	Duration of epilepsy	Age	Gender	History of perinatal or febrile seizures	Family history of epilepsy	Neurological deficit	Status epilepticus	Number of AEDs	Type of AEDS	Seizure type	Seizure frequency	Electroencephalogram	CT scan	Etiology	Education	Years of remission	Psychiatric disorder	Response to AED therapy	Age at relapse	Number of seizures	Trauma	Duration of AED therapy
Reference Total –ve correlations	**Year**	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	1	0	0	0	0

√ = relationship between this factor and seizure recurrence was assessed by study
† = Positive correlation observed
‡ = Negative correlation observed

Figure 7. Factors Assessed and their Association with Seizure Recurrence



Rationale for Key Question

As stated previously, time since last seizure appears to be inversely related to the risk for seizure recurrence in individuals treated with AEDs. The longer an individual remains seizure free while on an AED, the less likely it is that that individual will experience seizure recurrence. This risk factor is clearly recognized as being important by those concerned with road safety. This is evidenced by the fact that most current regulations and guidelines pertaining to the fitness of an individual who has experienced a seizure to be reissued with a driving permit consider the time since last seizure; often this is the only factor taken into consideration.

The purpose of this section of the report is to attempt to quantify the relationship between time since last seizure and the likelihood that a seizure will occur within the following year in individuals who are being treated successfully with an AED (as evidenced by being declared "seizure free"). Such information will allow FMCSA to make informed decisions about the risk that an individual who has been seizure free for a given period represents to him- or herself and other road users.

Identification of Evidence Base

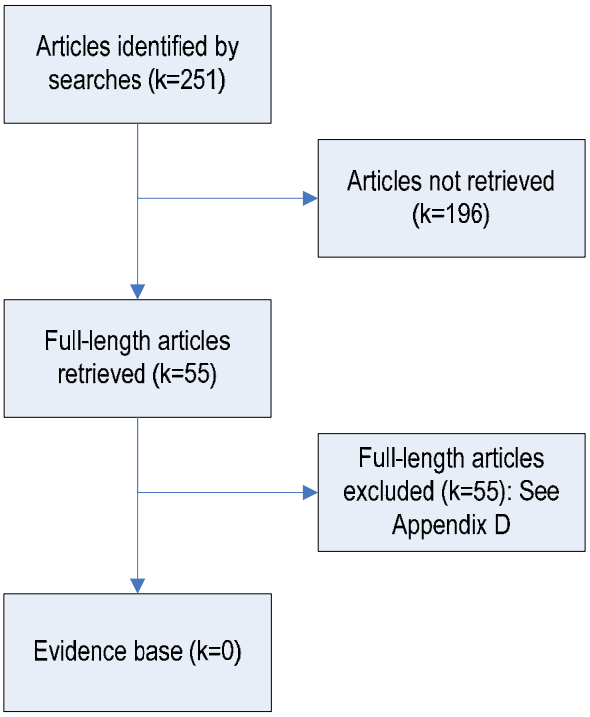
The primary objective of this section of the evidence report is to systematically review the evidence pertaining to the relationship between seizure recurrence likelihood and the time since last seizure among individuals who are currently on AED treatment and apparently seizure free. Our ultimate aim, should the available data allow it, is to develop a quantitative model describing

this relationship that will allow FMCSA to estimate the likelihood that an individual who has been seizure free for a certain period of time will experience seizure recurrence within the near future (1 year).

In attempting to meet the aims of this section, we searched for studies of any design that presented data on seizure recurrence as a function of time since last seizure (time-to-event data) obtained from individuals who were receiving AEDs. Our decision to consider studies regardless of their design was motivated by an awareness that relevant time-to-seizure recurrence data obtained from seizure free individuals on AED therapy may be difficult to identify.

The pathway by which the evidence base for Key Question 2 was determined is summarized in Figure 9. Our searches (Appendix A) identified a total of 251 articles that appeared to be relevant to this key question. Following application of the retrieval criteria for this question (Appendix B), 55 full-length articles were retrieved and read in full. Of these 55 retrieved articles, none of the articles were found to meet the inclusion criteria for this question (Appendix C). Table D 2 Appendix D lists the 55 articles that were retrieved but then excluded and provides rationale for their exclusion.

Figure 8. Development of Evidence Base for Key Question 2



None of the studies examined for inclusion in the evidence base for Key Question 2 reported time since last seizure as an index event, meaning that all the studies had to be excluded. The majority of retrieved studies (k=16) that were excluded were designed to investigate the impact of drug withdrawal on seizure recurrence, meaning that the individuals being observed were no longer using AED therapy.[10] The next largest group of studies comprised newly diagnosed

[10] *Determining whether a relationship exists between AED withdrawal and risk of seizure recurrence is beyond the scope of the current report, but will be investigated in a separate evidence report on seizures disorders to appear later.*

individuals who were beginning AED therapy to achieve seizure freedom (k=3), meaning that they had not yet experienced established seizure control. Two (k=2) studies included mixed populations of individuals who had withdrawn, were in the process of withdrawing, or were still utilizing AED therapy. Both of these studies used as inclusion criteria a minimum number of seizure-free years, meaning that the time since last seizure was not included in the evidence examined. One study (k = 1) contained a model which was too specific for inclusion in the evidence base. Another paper (k = 1) comprised a meta-analysis of seizure-prevention trials, and could not be included in the evidence base. The remainder of the excluded studies (k = 32) noted in Figure 8 were retrieved as background and reference documents. Therefore, no studies met the inclusion criteria for Key Question 2.

Evidence Base

No studies met the inclusion criteria for Key Question 2.

Findings

Because no studies identified by our searches met the inclusion criteria for Key Question 2, we cannot quantify the relationship between seizure recurrence and time since last seizure in individual with seizures disorder who were seizure free while receiving AED therapy.

Existing models

Currently there are no models available which aim to predict the likelihood of seizure recurrence solely for seizure-free individuals using AED therapy. However, a prognostic index for seizure recurrence related to AED therapy (continuous or withdrawn) has been developed by Chadwick et al.(116) This index is based on the results from the Medical Research Council Antiepileptic Drug Withdrawal Study Group (MRC) research and takes into consideration a number of specific factors which the MRC group recognized as appearing to influence the degree of risk of seizure recurrence, including: electro-clinical syndrome (i.e. benign rolandic epilepsy; juvenile myoclonic epilepsy), age at onset of disease, underlying etiology of disease, EEG, severity of epilepsy, and influence of individual medications. The original prognostic index described by Chadwick was recently expanded to create two models.(121) This update was made to accommodate the special considerations required for prediction of seizure recurrence for individuals presenting with first seizures and early epilepsy. These models appear in Table 26, Table 27, Table 28 and Table 29. For each model, the lower the final score, the lower the probability of seizure recurrence for the individual being assessed.

It should be noted that these models have yet (as of February 2007) to be validated by further research, and the use of these models to predict seizure recurrence should be viewed with appropriate caution.

Table 26. Prognostic model for prediction of seizure recurrence for first seizure and early epilepsy*

Seizure (number)	Score
One seizure at presentation	0
Two seizures at presentation	+1
Three or more seizures at presentation	+2
Add if any present • Neurological disorder / deficit, • learning disability • developmental delay	+ 1
Abnormal EEG	+1
Risk Classification Group for Seizure Recurrence	Add results of column to derive Final Score

*To obtain a final score (maximum=4) one simply adds the scores. If the total score is 0, then the risk for seizure recurrence is considered to be "low." If the total score is 1, the risk for seizure recurrence is assumed to be "Medium." If the score is >1 then the risk for recurrence is assumed to be "high." Having determined the risk stratification for an individual one now determines the probability for seizure recurrence at 1 year and 3 years in the future using Table 27.

Table 27. Probability for Seizure Recurrence by Risk Group (as Proposed by Chadwick)

Treatment Allocation by Risk of Seizure Recurrence	Probability of Seizure by 1 year	Probability of Seizure by 3 years
Medium risk of Seizure Recurrence Start immediate AED treatment Delay AED treatment	 0.23 0.34	 0.34 0.48
High Risk of Seizure Recurrence Start immediate AED treatment Delay AED treatment	 0.35 0.57	 0.46 0.67

Table 28. Factors for the calculation of a prognostic index for seizure recurrence by 1 and 2 years following continued treatment or slow withdrawal of antiepileptic drugs, in patients with a minimum remission of seizures lasting for 2 years while on treatment*

Factor	Value to be added to the Score	
1.Starting score for all patients	-175	
Age > 16 years	45	
Taking more than 1 AED	50	
Seizures occurring after the start of treatment	35	
History of any tonic-clonic seizure (generalized or partial in onset)	35	
History of myoclonic seizures	50	
EEG while in remission Not Done Abnormal	 15 20	
Duration of seizure-free period (years) = D	200/D	
2.Total Score is represented by:	T	
3.Exponentiate T/100 ($Z = e^{T/100}$)	Z	

*To obtain a final score, add together the scores in rows beginning with the 'starting scores for all patients' and continuing through the row beginning with 'duration of seizure-free period (years) = D' to achieve the total score (T). Factor this score as directed in Step 3 to obtain a z score. Having determined the risk stratification for the individual, one now determines the probability for seizure recurrence at 1 and 2 years in the future using Table 29.

Table 29. Probability for Seizure Recurrence in Patients Seizure Free for 2 yrs

Treatment allocation	Probability of Seizure Recurrence By 1 year	Probability of Seizure Recurrence By 2 years
On continued treatment	$1 - 0.89^{Z}$	$1 - 0.79^{Z}$
On slow withdrawal of treatment	$1 - 0.69^{Z}$	$1 - 0.60^{Z}$

Section Summary

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 reoccur 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. 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?

Introduction

As stated in the Background section of this report, the goal of epilepsy surgery is either to define and resect an area of epileptogenesis or disrupt the spread of seizure activity in order to reduce the likelihood of seizures or prevent certain seizure types. For the purposes of FMCSA, only those surgical procedures that have been shown to lead to remission from seizures are of interest. Individuals who undergo palliative treatment will continue to have seizures, albeit at a reduced rate, and they will not be considered for a commercial driver's license.

Although approximately two thirds of individuals who undergo the most common types of surgery for epilepsy become seizure free a significant proportion of these individuals will experience seizure recurrence. Several studies have noted that the likelihood of an individual experiencing seizure recurrence following surgery decreases as a function of increasing time since last seizure.(122-127) In other words, an individual who has been seizure free for five years is less likely to experience seizure recurrence in the near future than an individual who has

only been seizure free for one year. In this section of the Evidence Report we identified studies that attempted to quantify this relationship with the aim of developing a model (or models) that would predict the probability that an individual who has been seizure free for any given period of time will experience seizure recurrence within the following year.

Identification of Evidence Base

The identification of the evidence base for Key Question 3 is summarized in Figure 9. Our searches (Appendix A) identified a total of 227 articles that appeared to be relevant to this key question. Following application of the retrieval criteria (Appendix B) for this question, 35 full-length articles were retrieved and read in full. Of these 35 retrieved articles, 12 articles were found to meet the inclusion criteria (Appendix C) for Key Question 3. Table D-3 of Appendix D lists the 23 articles that were retrieved but then excluded and provides rationale for their exclusion. Table 30 lists the 12 articles that met the inclusion criteria for Key Question 3.

Figure 9. Development of Evidence Base for Key Question 3

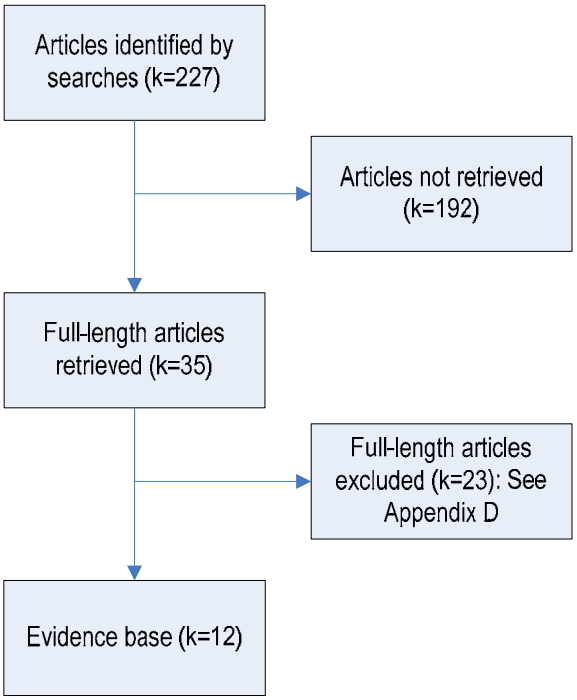


Table 30. Evidence Base for Key Question 3

Reference	Year	Study Location	Country
Jeha et al.(128)	2006	Cleveland, Ohio	USA
Kelly et al.(129)	2005	Bethesda, Maryland	USA
Spencer et al.(126)	2005	New Haven, CT; Los Angeles CA; Philadelphia, PA; New York, NY; Bronx, NY; Minnesota, MN	USA
McIntosh et al.(130)	2004	Melbourne, Victoria	Australia

Reference	Year	Study Location	Country
Yoon et al.(131)	2003	New Haven, CT	USA
Jutila et al.(132)	2002	Kuopio	Finland
Foldvary et al.(124)	2000	Durham, NC	USA
Salanova et al.(123)	1999	Indianapolis. Indiana	USA
Eliashiv et al.(133)	1997	Los Angeles, CA	USA
So et al.(122)	1997	Rochester, MN	USA
Luders et al.(134)	1994	Cleveland, Ohio	USA
Rougier et al.(135)	1992	Bordeaux	France

Evidence Base

This subsection provides a brief description of the key attributes of the 12 studies that comprise the evidence base for Key Question 3. Here we discuss pertinent information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of commercial vehicles. Detailed information pertinent to this section that has been extracted from included studies is presented in the *Study Summary Tables* that can be found in Appendix G.

Characteristics of Included Studies

The primary characteristics of the 12 included studies that address Key Question 3 are presented in Table 31. 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.

Table 31. Key Study Design Characteristics of Studies that Address Key Question 3

Reference	Year	Design	Prospective?	Number of centers	Sample Size (N=)	Period during which surgery performed	Method by which seizure status collected?	Method of analysis	Number of individuals at risk at each time point reported?	Median time-to-event presented?	Hazard rate of hazard function presented described?	Followup time
Jeha et al.(128)	2006	Case Series	No	1	371	1990 to 2001	Clinic visits or phone calls	Hazard modeling to predict time to first seizure recurrence	Yes	No	No	Mn: 5.5 yrs Rng: 1 to 14.4 yrs
Kelly et al.(129)	2005	Case Series	No	1	56	1966 to 1974	Telephone interviews were conducted with patients, family members, and occasionally patients' neurologists. Written questionnaires were sent to each patient.	Time to event data plotted using Kaplan-Meier curves.	No	Yes. Can be obtained from KM curve	No	Mn: 29.9 yrs SD: 4.9 yrs
Spencer et al.(126)	2005	Case Series	Yes	7	339	1996 to 2001	Information on preoperative historical factors was obtained from medical record review and from patient interview at baseline. Post-surgically, patients were called every 3 months to ascertain seizure frequency.	Bivariate analyses were performed with Chi-squared tests and tests for trend when appropriate. Proportional hazards analysis used to estimate bivariate rate ratios. Some findings displayed as Kaplan Meier curves. For multivariate analysis, authors used a proportional hazards model.	No	No	No	Mdn: 4.6 yrs Rng: 2 to 7.3 yrs
McIntosh et al.(130)	2004	Case Series	No	1	325	1978 to 1998	Hospital notes. Follow-up conducted bi-annually by telephone for patients who had not had contact with Austin Health in the previous 2 years. Patients treated prior to 1986 who had not remained patients at Austin Health contacted by telephone, and seizure history since last follow-up reviewed.	Time to event data plotted using Kaplan-Meier curves. Multivariate regression performed using Cox proportional hazard models.	No	Yes. Can be obtained from KM curve	No	Mn: 9.6 yrs SD: 4.2 yrs
Yoon et al.(131)	2003	Case Series	No	1	175	1972 to 1992	Data abstracted from medical records When follow-up data within the last year was unavailable in the charts authors attempted to locate and interview patients by telephone.	*t*-tests to analyze continuous variables. Chi-squared test to examine categorical variables. Time-to-event data plotted using Kaplan-Meier curves. Multivariate regression performed using Cox proportional hazard models.	No	Yes. Can be obtained from KM curve	No	Mn: 8.4 yrs
Jutila et	2002	Case	No	1	140	1988 to 1999	Medical records	Data analyzed using c2 test for	Yes	No	No	Mn: 5.4 yrs

Reference	Year	Design	Prospective?	Number of centers	Sample Size (N=)	Period during which surgery performed	Method by which seizure status collected?	Method of analysis	Number of individuals at risk at each time point reported?	Median time-to-event presented?	Hazard rate of hazard function presented described?	Followup time
al.(132)		Series						comparisons between patient groups, and with life tables.				SD: 2.6 yrs
Foldvary et al.(124)	2000	Case Series	No	1	79	1962 to 1984	Medical records and by telephone interview with patient or family member if possible	Time to event data plotted using Kaplan-Meier curves.	No	Yes. Can be obtained from KM curve	No	Mn: 14 years Rng: 2.1 to 31.6 yrs
Salanova et al.(123)	1999	Case Series	No	1	145	1984 to 1995	Medical records	Time to event data plotted using "actuarial" curves.	Yes	No	No	Mn: 5.6 yrs Rng: 2 to 12 yrs
Eliashiv et al.(133)	1997	Case Series	No	1	60	1963 to 1992	Medical records and by telephone interview with patient or family member if possible	Time to event data plotted using Kaplan-Meier curves. Different curves compared using log-rank test	No	No	No	Mn: 8.4 yrs Rng: 1 to 30 yrs
So et al.(122)	1997	Case Series	No	1	184	1988 to 1991	Medical records	Change from last time point assessed using t-tests.	Yes	No	No	Mn: NR Rng: NR to 5.7 yrs
Luders et al.(134)	1994	Case Series	No	1	71	NR	Medical records	Data analyzed using c2 test for comparisons between patient groups	Yes	No	No	> 2 years
Rougier et al.(135)	1992	Case Series	Not clear	1	100	1980 to 1990	Not clear	Time to event data plotted using "actuarial" curves. Markov Models also produced that took into consideration fact that individuals can become seizure free again	Yes	No	No	NR

*Crash estimates calculated using a prevalence estimate for epilepsy of 5.1/1,000 from National Center for Health Statistics and Census data for adults 18 years and older

†Group contains additional individuals who do not meet the typical definition of epilepsy

Mdn=Median; Mn=Mean; Rng=Range; SD=Standard deviation;

Quality of Included Studies

The findings of our assessment of the quality of these studies are presented in Table 32. Our assessment of the quality of the studies that comprise the present evidence base found that the overall quality of the included studies was low (Median Quality Score=6.25; Quality=Low). Aside from poor reporting which made evaluation of study quality difficult in many cases, the primary reasons for the low quality scores was due to the fact that all studies were case-series (single arm observational studies), and that data was collected retrospectively in 11 of the twelve studies.

Table 32. Quality of the studies that Assess Key Question 3

Reference	Year	Quality Scale Used	Quality Score	Quality
Jeha et al.(128)	2006	ECRI Quality Scale X:: Case-series-time-to-event studies	6.1	Low
Kelly et al.(129)	2005	ECRI Quality Scale X:: Case-series-time-to-event studies	4.3	Low
Spencer et al.(126)	2005	ECRI Quality Scale X:: Case-series-time-to-event studies	8.2	Moderate
McIntosh et al.(130)	2004	ECRI Quality Scale X:: Case-series-time-to-event studies	5.7	Low
Yoon et al.(131)	2003	ECRI Quality Scale X:: Case-series-time-to-event studies	6.4	Low
Jutila et al.(132)	2002	ECRI Quality Scale X:: Case-series-time-to-event studies	6.4	Low
Foldvary et al.(124)	2000	ECRI Quality Scale X:: Case-series-time-to-event studies	7.5	Low
Salanova et al.(123)	1999	ECRI Quality Scale X:: Case-series-time-to-event studies	7.5	Low
Eliashiv et al.(133)	1997	ECRI Quality Scale X:: Case-series-time-to-event studies	6.8	Low
So et al.(122)	1997	ECRI Quality Scale X:: Case-series-time-to-event studies	5.2	Low
Luders et al.(134)	1994	ECRI Quality Scale X:: Case-series-time-to-event studies	5.9	Low
Rougier et al.(135)	1992	ECRI Quality Scale X:: Case-series-time-to-event studies	5.9	Low

From the perspective of one who wishes to pool time-to-seizure recurrence data from the included studies with the aim of developing a model that will predict seizure recurrence given a specific seizure free period, the incomplete reporting of these data severely affects the methodologies that are available. For example, information on censoring was not presented in a single article (though in a few cases one can estimate this from information on the number of patients at risk at a particular time point). Other information such as median event time, hazard rate, hazard function, etc that would allow for the pooling of time-to-event data across studies using standard techniques were also rarely presented.

Generalizability of Evidence to Target Population

The purpose of this subsection is to provide details of the extent to which the individuals enrolled in the studies that address Key Question 3 are similar to CMV drivers in the United States. Important characteristics of the individuals included in the studies that address Key Question 3 are presented in Table 33.

Given current regulations pertaining to driving a CMV and epilepsy, it is unlikely that the individuals enrolled in any of the included studies are representative of individuals who drive this class of vehicle. Having said this, the purpose of this question is to determine whether individuals with epilepsy who have undergone surgical treatment might be considered for a CDL by virtue of having an acceptably low seizure risk. From this standpoint, the generalizability of outcome data from the 12 included studies to individuals who wish to apply for a commercial motor vehicle is unclear.

When compared to the CMV driver population, which are predominantly 35 to 45 year old males, younger individuals and females are overrepresented in the included studies.

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.(126,131,135) 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.

The ideal outcome from surgery for epilepsy is that an individual will achieve seizure freedom even after AED withdrawal. It is common practice among many centers to attempt AED withdrawal following a post-surgical seizure free period of 2-years. While some individuals enrolled in all 12 studies were withdrawn from AEDs during the follow up, most investigators did not report on the proportion of enrollees in which AED withdrawal was attempted. This presents an important limitation to our analysis because withdrawal from antiseizure medication appears to be a significant risk factor for seizure recurrence.(127,130) Consequently, one would expect that differences across studies in the proportion of individuals in whom AED withdrawal was attempted may result in important between studies differences in seizure recurrence rates (heterogeneity).

Table 33. Generalizability of Studies that Address Key Question 3

Reference	Year	Type(s) of epilepsy	Duration of epilepsy	Minimum seizure free period	% Male	Type of Surgery	Age in yrs	% withdrawn from AEDs	Driving exposure	% with medically restricted licenses?	% CMV drivers	Generalizability to target population
Jeha et al.(128)	2006	Medically refractory TLE	NR	NR	NR	Selective amygdalohippocampectomy (n=52) Removal of mesial structures, temporal tip, and parahippocampal and inferior temporal gyri (n=266) Neocortical resection (n=53)	NR	20.8	NR	NR	NR	Unclear
Kelly et al.(129)	2005	Medically refractory TLE	Left temporal: 20.1 (9.7) years Right temporal: 16.5 (7.6) years	NR	NR	Temporal lobectomy (n=48) Left temporal (n=22) Right temporal (n=26)	Mn (SD): 32.4 (11.5) (left temporal) Mn (SD): 25.9 (7.1) (right temporal)	NR	NR	NR	NR	Unclear
Spencer et al.(126)	2005	Localization-related epilepsy	Mesial temporal lobe resection < 5 yrs, n=15 5-9 yrs, n=36 10-14 yrs, n=43 15-19 yrs, n=39 ≥ 20 yrs, n=164 Resections in neocortical regions NR	2 years	NR	Mesial temporal lobe resection (n=297) Resections in neocortical regions (n=42)	Mesial temporal lobe resection 12-19, n=22 20-29, n=50 30-39, n=101 40-49, n=81 ≥ 50, n=43 Resections in neocortical regions NR	NR	NR	NR	NR	Unclear
McIntosh et al.(130)	2004	Medically refractory TLE	NR	NR	NR	Anterior temporal lobectomy (n=325) Right-sided surgery (n=145)	NR	31%	NR	NR	NR	Unclear
Yoon et al.(131)	2003	Medically intractable localized epilepsy	< 20 yrs, n=108 20-30 yrs, n=42 > 30 yrs, n=20	1 year	52	Right-sided surgery (n=78) Lobe resected Temporal only (n=140) Temporal plus (n=7) Frontal only (n=12) Frontal plus (n=1) Parietal only (n=5) Parietal plus (n=3) Occipital only (n=7)	3-12, n=2 13-19, n=34 20-29, n=67 ≥ 30, n=71	NR	NR	NR	NR	Unclear

Reference	Year	Type(s) of epilepsy	Duration of epilepsy	Minimum seizure free period	% Male	Type of Surgery	Age in yrs	% withdrawn from AEDs	Driving exposure	% with medically restricted licenses?	% CMV drivers	Generalizability to target population
Jutila et al.(132)	2002	Medically refractory TLE (n=140) Unilateral temporal lobe epilepsy (n=103)	Median: 19 (range, 2-47) years	NR	52	Anterior temporal resection and amygdalohippocampectomy alone (n=113) Anterior temporal resection and amygdalohippocampectomy combined with lesionectomy (n=9) Selective amygdalohippocampectomy (n=18)	Mdn: 32 (rng, 14-54)	NR	NR	NR	NR	Unclear
Salanova et al.(123)	1999	Medically refractory TLE	Mean: 19.7 (range, 1–-45) years	NR	NR	Most individuals underwent en bloc temporal lobectomy by the same neurosurgeon, including the lateral and mesial temporal structures, and a few had lesionectomy and resection of the epileptogenic zone.	Mn: 30.4 (rng, 8–53)	18%	NR	NR	NR	Unclear
So et al.(122)	1997	Medically Intractable complex partial epilepsy	Median: 19.5 years	NR	45.3	Anterior temporal lobectomy with amygdalohippocampectomy All individuals underwent the same technique for resection of the lateral temporal cortex and the mesial temporal structures, which included the amygdala, the hippocampus and the parahippocampal gyrus.	Mdn: 31	NR	NR	NR	NR	Unclear
Eliashiv et al.(133)	1997	Medically refractory TLE	Mean: 13 years	NR	45	All individuals underwent uniform en bloc temporal lobe resection. This procedure included resection of the lateral neocortex (approximately 4.5 cm in the dominant hemisphere and 6 cm in the nondominant hemisphere) and mesial cortex, including 3 cm of the hippocampus. Forty-one patients had surgery on the right hemisphere and 19 0n the left.	NR	NR	NR	NR	NR	Unclear
Foldvary et al.(124)	2000	Medically refractory TLE	Mean (SD): 12.9 (8.5) years	NR	57	Temporal lobectomy Left temporal resections were performed in 57% of individuals.	Mn: 23.9 (SD: 9)	35%	NR	NR	NR	Unclear
Luders et al.(134)	1994	Medically refractory TLE	NR	NR	62	Right temporal resection (n=28) Left temporal resection (n=29) Extratemporal resection (n=11)	NR	NR	NR	NR	NR	Unclear
Rougier et al.(135)	1992	Temporal (n=76), frontal (n=23), and parietal (n=1) lobe epilepsies	Mean: 13 (range, 2-40) years	NR	59	Seventy-six temporal lobe epileptics had cortical resection ranging from lobectomy (n=50) to amygdalohippocampectomy (n=23). Resection was limited to the posterolateral temporal cortex in 3 cases. Frontal lobe epilepsies (n=23), 9 lobectomies	Mn: 29 (rng, 3-59)	NR	NR	NR	NR	Unclear

Reference	Year	Type(s) of epilepsy	Duration of epilepsy	Minimum seizure free period	% Male	Type of Surgery	Age in yrs	% withdrawn from AEDs	Driving exposure	% with medically restricted licenses?	% CMV drivers	Generalizability to target population
						and 14 more restricted cortical resections were performed (5 in the pre-frontal region; 3 in the supplementary motor area; 3 in the pre-motor area; and 3 in the orbitofrontal area). One cortical resection concerned the parietal opercular convolutions in the non-dominant hemisphere.						

Mdn=median; Mn=mean; NR=not reported; rng=range; SD=standard deviation; TLE=temporal lobe epilepsy; yrs=years

Findings

Data on the cumulative probability for seizure recurrence extracted from the 12 included studies are presented in Table 34.

Table 34. Cumulative Probability of Seizure Recurrence

Reference	Year	Type of Surgery	Landmark event	Followup time (Years)											
				1	2	3	4	5	6	7	8	9	10	15	20
Jeha et al.(128)	2006	Temporal lobectomy	Surgery	-	0.24	-	-	0.34	-	-	0.42	-	0.47	-	-
Kelly et al.(129)	2005	Temporal lobectomy	1 year	0.00	0.33	0.48	0.52	0.58					0.63	0.67	0.67
Spencer et al.(126)	2005	Temporal lobectomy or other neocortical resections	2 years	-	0.00	0.13	0.23	0.30	-	-	-	-	-	-	-
McIntosh et al.(130)	2004	Temporal lobectomy	Surgery	0.29	0.45	-	-	0.52	-	-	-	-	0.59	0.63	-
Yoon et al.(131)	2003	Temporal, frontal, parietal or occipital lobectomy	1 year	0.00	0.11	0.16	-	0.27	-	-	-	-	0.43	-	-
Jutila et al.(132)	2002	Temporal lobectomy	1 year	0.00	0.34	0.42	0.46	0.50	-	0.55	-	-	-	-	-
Salanova et al.(123)	1999	Temporal lobectomy	Surgery	0.31	0.34	0.37	0.37	0.37	0.37	0.40	0.42	0.42	0.42	-	-
So et al.(122)	1997	Temporal lobectomy	Surgery	0.35	0.34	0.35	0.35	0.41	-	-	-	-	-	-	-
Eliashiv et al.(133)	1997	Temporal lobectomy	Surgery	0.02	0.04	0.10	0.14	0.18	0.2	0.2	0.2	0.22	0.24	-	-
Foldvary et al.(124)	2000	Temporal lobectomy	Surgery	0.37	0.47	-	-	0.48	-	0.50	-	-	0.50	-	-
Luders et al.(134)	1994	Temporal lobectomy	Surgery	0.25	0.34	-	-	-	-	-	-	-	-	-	-
Rougier et al.(135)	1992	Temporal or frontal or parietal or occipital lobectomy	Surgery	0.38	0.45	0.50	0.53	0.55	0.58	-	-	-	-	-	-

From an examination of Table 34, it is apparent that the cumulative probability that an individual who is seizure free following surgery for focal epilepsy will experience seizure recurrence increases as a function of time. Also apparent from the table is that the incremental probability (the probability for seizure recurrence during a finite period in the future) decreases as a function of increasing seizure free period. In other words, the longer one is seizure free, the lower the risk for experiencing seizure recurrence in the near future.

Below we report on our synthesis of data presented in Table 34 with the aim of developing a model which describes the relationship between the likelihood of experiencing seizure recurrence and seizure free period. Such a model, should it be successfully developed and tested, will be useful to FMCSA and its medical examiners because it will allow predictions to be made about the likelihood that an individual who has been seizure free following surgery for a specific period, will experience seizure recurrence in the near future.

Protocol Used in Analysis of Data Presented in Table 34

As mentioned in the *Methods* section, we addressed Key Question 3 by attempting to determine a summary time-to-event (survival) function from relevant data extracted from 12 included studies. In brief, survival data were pooled using non-linear regression. The survival function for each individual study was fit by a mathematical model based on one of several possible probability distributions (exponential, Weibull, etc). All that is required by the technique is that the proportion of seizure free individuals at a number of time points be known. The protocol used to analyze the time-to-event data extracted from the 12 included studies is presented below:

1. Data were examined to identify the distribution from which they originate
2. Individual survival curves were fit to data from each included study using the appropriate distribution
3. A hazard function (λ) and its 95% confidence intervals were derived for each study from its survival curve
4. The hazard functions for each study were combined meta-analytically using a random effects model in order to determine an average hazard function that summarizes the data from all 12 studies
5. An average survival function was derived from the average hazard function
6. The summary survival function was used to investigate the likelihood that an individual who had been seizure free for a particular period will experience seizure recurrence in the following year.

The Survival Function and its Derivatives

The object of the primary interest in addressing Key Question 3 is the survival function. The survival function is conventionally denoted *S(t)* and is defined as follows:

$$S(t) = \Pr(T > t)$$

where, t is time (in this case time since last seizure), T is the time of an event (in this case seizure recurrence), and "Pr" stands for probability. Usually one assumes that the probability of an event not occurring prior to time 0 is 1 (*S[0]* = 1), although the probability could be less than 1 if there is the possibility of immediate seizure recurrence. A feature of the survival function is that it must be non-increasing: $S(u) \leq S(t)$ if u > t. This is important because it expresses the notion that the time-to-an event can only become less probable as time increases. Thus, the use of a survival curve to describe the relationship between the probability for seizure recurrence as a function of the time since last seizure is valid *only* if the probability for seizure recurrence reduces as a function of the time since last seizure. In other words, by fitting a survival curve to the data

collected as part of Key Question 3, one implicitly assumes that the longer the time since last seizure, the less likely seizure recurrence becomes.

The survival probability is usually assumed to approach zero as time increases without bound, i.e., $S(t) \rightarrow 0$ as $t \rightarrow \infty$. However, when used to describe the relationship between seizure recurrence and the time since last seizure, it is possible that some individuals will be cured by surgery and never experience a seizure again. Consequently, rather than approach 0, the survival probability will approach a plateau that is >0 as time increases without bound, i.e., $S(t) \rightarrow$ Plateau as $t \rightarrow \infty$.

Several related quantities are defined in terms of the survival function. These are the cumulative distribution function (*F[t]*), the hazard function (*h[t]*) and the cumulative hazard function ($\Lambda(t)$).

By convention, *F(t)* is defined as the compliment of the survival function:

$$F(t) = \Pr(T \leq t) = 1 - S(t)$$

and the derivative of *F(t)* (i.e., the density function of the cumulative distribution) is conventionally denoted as *f(t)*:

$$f(t) = \frac{d}{dt} F(t)$$

The hazard function (λ), is defined as the event rate at time t conditional on survival until time t or later:

$$\lambda(t)\,dt = \Pr(t < T < t + dt \,|\, T > t) = \frac{f(t)\,dt}{S(t)} = -\frac{S'(t)\,dt}{S(t)}$$

The hazard function can alternatively be represented in terms of the cumulative hazard function, conventionally denoted Λ:

$$\Lambda(t) = -\log S(t)$$

So,

$$\frac{d}{dt}\Lambda(t) = -\frac{S'(t)}{S(t)} = \lambda(t)$$

$\Lambda(t)$ is typically called the cumulative hazard function because the preceding definitions together imply

$$\Lambda(t) = \int_0^t \lambda(u)\,du$$

which is the "accumulation" of the hazard over time.

Survival distributions

Survival models are constructed by choosing a basic survival distribution. The choice of survival distribution one chooses expresses some particular information about the relation of time (and any exogenous variables) to the event of interest (seizure recurrence). It is natural to choose a

statistical distribution which is non-negative since survival times are non-negative. The most common distributions used for survival modeling are the exponential[11], gaussian, and log-normal distributions (Table 35).

Table 35. Formulae for Exponential, Weibull and Log Normal Distributions

Exponential (special case of Weibull)	$e^{-t/\lambda}$
Weibull	$e^{-(t/\lambda)^k}$
Lognormal	$\frac{1}{2}\left(1 - \mathrm{Erf}\left[\frac{\ln(t)-\mu}{\sigma\sqrt{2}}\right]\right)$

The survival data extracted from the 12 included studies that addressed Key Question 3 most likely come from one of these distributions. The first stage of our analysis was to determine which of these distributions best fits our data.

Determination of Distribution that Best Describes Available Survival Curves

The Exponential Distribution

The simplest distribution from which survival data originate is the exponential distribution. The cumulative distribution, survivorship, and hazard functions for this distribution are presented in Table 36.

Table 36. Formulae for Cumulative Distribution, Survival, and Hazard Functions

Function	Formula	
Cumulative Distribution Function	$F(t) = 1 - e^{-\lambda t}$	t ≥ 0
Survival Function	$S(t) = e^{-\lambda t}$	t ≥ 0
Hazard Function	$h(t) = \lambda$	t ≥ 0

As shown above, the exponential distribution is characterized by a single parameter, the constant hazard rate, λ. In the context of this report, a high λ indicates that the chances of experiencing seizure recurrence are high and a long seizure free period is unlikely. A low λ on the other hand indicates that the chance of experiencing seizure recurrence is low and that a long seizure free period is to be expected. It is important to note that the hazard rate underpinning this survival data remains constant as a function of time. That is, the risk for seizure recurrence follows a purely random pattern.

To test whether the survival data reported by the studies included in the evidence base for Question 3 have an exponential distribution, we fitted the natural log of *S(t)* for each data set against follow up time with a linear regression model (Figure 10) and tested the goodness of fit

[11] Note that the exponential distribution is a special case of the Weibull distribution

of the model (Table 37). These analyses found that the survival curves for all 12 included studies appeared to be well fit by a survival curve that is described by an exponential distribution.

Figure 10. Ln*S(t)* as a Function of Time

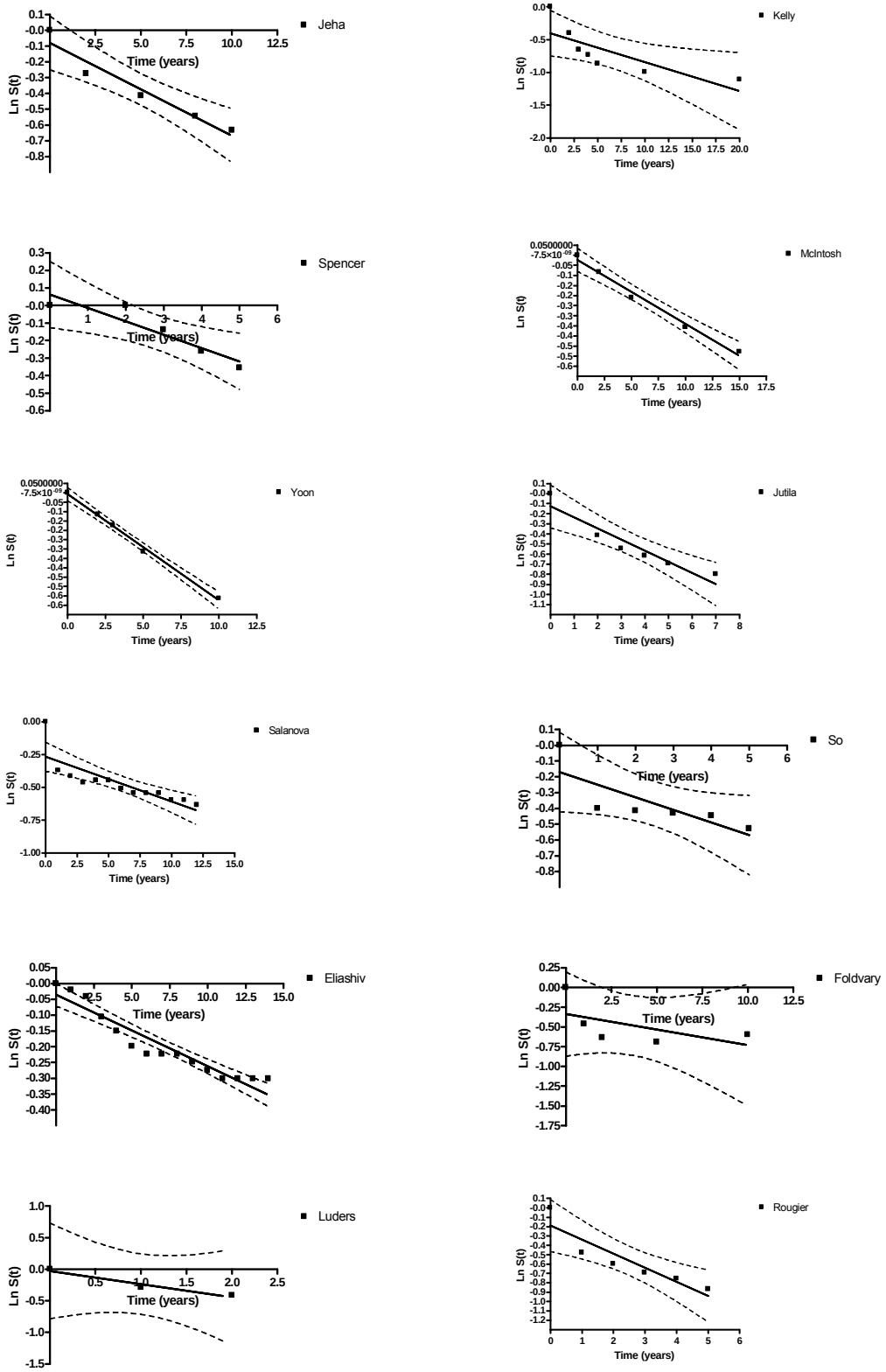


Table 37. Test of Assumption that S(t) Drawn from Exponential Distribution (Ln*S(t)* as a Function of Time)

Best-fit values	Jeha	Kelly	Spencer	McIntosh	Yoon	Jutila	Salanova	So	Eliashiv	Foldvary	Luders	Rougier
Slope (SD)	-0.05861 (0.008619)	-0.04412 (0.01523)	-0.07609 (0.01809)	-0.03172 (0.002160)	-0.05673 (0.002090)	-0.1101 (0.01862)	-0.03415 (0.007097)	-0.07974 (0.03000)	-0.02267 (0.002029)	-0.03956 (0.03292)	-0.2078 (0.04614)	-0.1504 (0.03297)
Y-intercept when X=0.0 (SD)	-0.08088 (0.05355)	-0.4025 (0.1355)	0.06160 (0.05944)	-0.02273 (0.01818)	-0.006961 (0.01098)	-0.1261 (0.07713)	-0.2656 (0.05019)	-0.1708 (0.09082)	-0.03545 (0.01669)	-0.3352 (0.1678)	-0.02664 (0.05957)	-0.1893 (0.09982)
X-intercept when Y=0.0	-1.3800	-9.1240	0.8095	-0.7164	-0.1227	-1.1460	-7.7770	-2.1420	-1.5640	-8.4720	-0.1282	-1.2590
1/slope	-17.0600	-22.6700	-13.1400	-31.5200	-17.6300	-9.0850	-29.2800	-12.5400	-44.1100	-25.2800	-4.8130	-6.6490
95% Confidence Intervals												
Slope	-0.08603 to -0.03118	-0.08328 to -0.004958	-0.1337 to -0.01854	-0.03860 to -0.02485	-0.06338 to -0.05008	-0.1617 to -0.05839	-0.04977 to -0.01853	-0.1630 to 0.003536	-0.02705 to -0.01829	-0.1443 to 0.06518	-0.7941 to 0.3786	-0.2419 to -0.05887
Y-intercept when X=0.0	-0.2513 to 0.08951	-0.7509 to -0.05414	-0.1276 to 0.2508	-0.08056 to 0.03511	-0.04190 to 0.02798	-0.3402 to 0.08801	-0.3761 to -0.1551	-0.4229 to 0.08136	-0.07149 to 0.0005937	-0.8692 to 0.1989	-0.7836 to 0.7303	-0.4664 to 0.08782
X-intercept when Y=0.0	-7.461 to 1.124	-132.0 to -0.7461	-5.895 to 2.190	-3.089 to 0.9548	-0.8139 to 0.4537	-5.496 to 0.5769	-19.62 to -3.224		-3.814 to 0.02249			-7.330 to 0.3923
Goodness of Fit												
r^2	0.9391	0.6266	0.8550	0.9863	0.9959	0.8973	0.6780	0.6385	0.9057	0.3250	0.9530	0.8388
Sy.x	0.0711	0.2537	0.0696	0.0264	0.0159	0.1011	0.0958	0.1255	0.0339	0.2658	0.0653	0.1379
Is slope significantly non-zero?												
F	46.2400	8.3900	17.7000	215.7000	736.9000	34.9500	23.1600	7.0660	124.9000	1.4440	20.2700	20.8100
DFn, DFd	1, 3	1, 5	1, 3	1, 3	1, 3	1, 4	1, 11	1, 4	1, 13	1, 3	1, 1	1, 4
P value	0.0065	0.0339	0.0245	0.0007	0.0001	0.0041	0.0005	0.0565	< 0.0001	0.3156	0.1391	0.0103
Deviation from zero?	Sig	Sig	Sig	Sig	Sig	Sig	Sig	NSig	Sig	NSig	NSig	Sig
Deviation from Model (Runs test)												
Points above line	3.0000	3.0000	2.0000	3.0000	4.0000	2.0000	5.0000	3.0000	6.0000	2.0000	2.0000	3.0000
Points below line	2.0000	4.0000	3.0000	2.0000	1.0000	4.0000	8.0000	3.0000	9.0000	3.0000	1.0000	3.0000
Number of runs	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000
P value (runs test)	0.5000	0.2000	0.5000	0.5000	1.0000	0.4000	0.0101	0.3000	0.0030	0.5000	1.0000	0.3000
Significantly nonlinear?	NSig	NSig	NSig	NSig	NSig	NSig	Sig	NSig	Sig	NSig	NSig	NSig

The Weibull Distribution

The Weibull distribution is a generalization of the exponential distribution. Unlike the exponential distribution, however, the Weibull distribution does not assume a constant hazard rate. The Weibull distribution is characterized by two parameters; the shape parameter (γ) and a scaler (λ). The cumulative distribution, survivorship, and hazard functions for this distribution are presented in Table 38.

Table 38. Formulae for Cumulative Distribution, Survival, and Hazard Functions

Function	Formula
Cumulative Distribution Function	$F(t) = 1 - e^{-\lambda t^{\gamma}}$ $t \geq 0$
Survival Function	$S(t) = e^{-\lambda t^{\gamma}}$ $t \geq 0$
Hazard Function	$h(t) = \lambda\gamma(\lambda\gamma)^{\gamma-1}$ $t \geq 0$

To test whether the survival data reported by the studies included in the evidence base for Question 3 have a gaussian distribution we tested the goodness of fit of the model (Table 39). These analyses found that the survival curves for 10 of the 12 included studies could be fit by a survival curve described by a gaussian distribution.

Which Model Best Fits Data?

Although it is clear that the survival curves from the 12 included studies can all be described by a function drawn from an exponential distribution, whereas only 10 of the 12 can be fit by a Weibull distribution in cases where both models fit the data, it is not clear which model provides the best fit. To determine this we used the "comparison of fits" function from the software package, "GraphPad Prism 4." This analysis, the results of which are presented in Table 40, found that the exponential distribution provided the best fit. Consequently, we continued our analysis using functions derived using the exponential distribution. The survival function (*S[t]* as a function of t) based on the exponential distribution for each of the 12 included studies is presented in Figure 11.

Table 39. Test of Assumption that that *S(t)* Drawn from Weibull Distribution

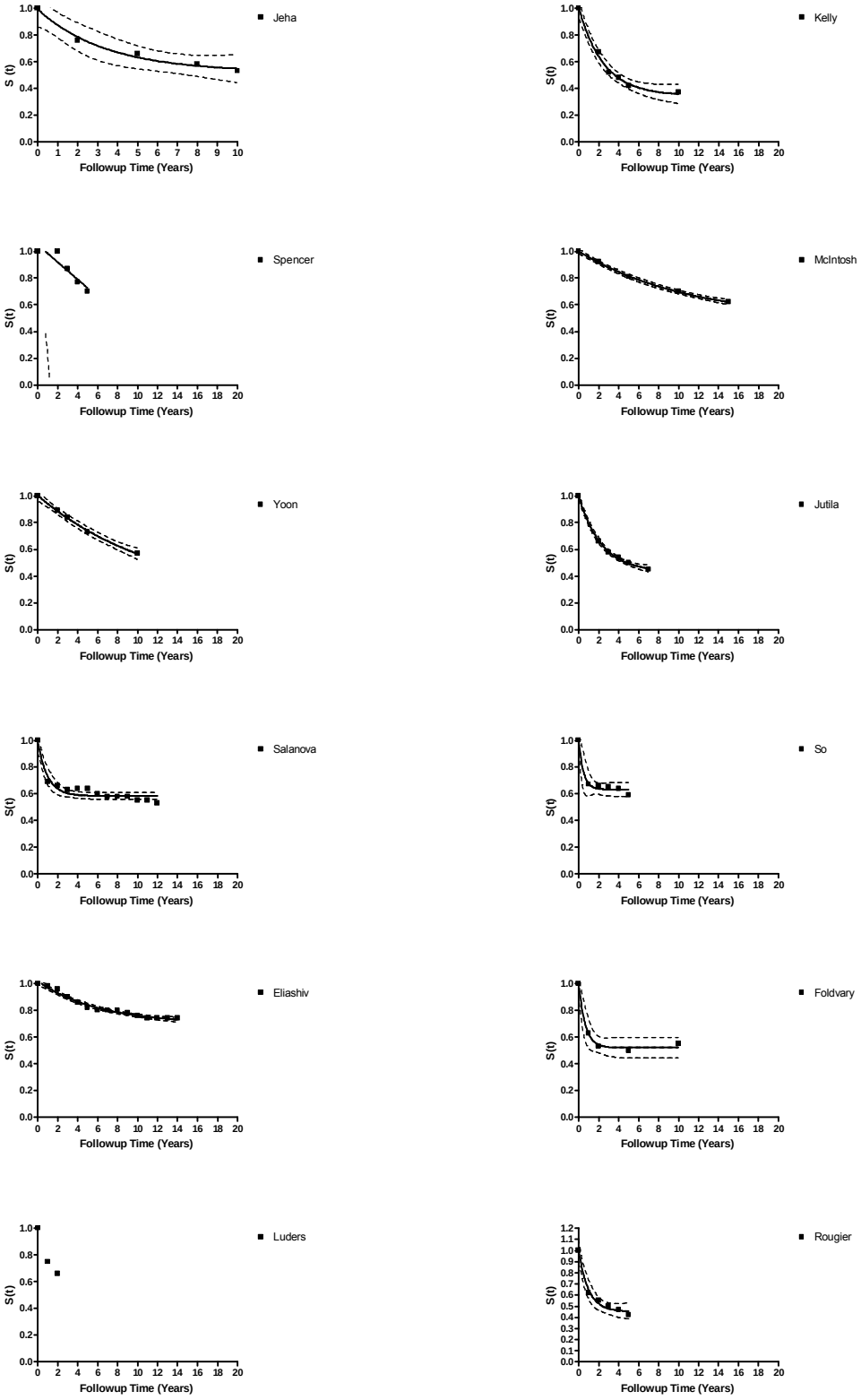
Best-fit values	Jeha	Kelly	Spencer	McIntosh	Yoon	Jutila	Salanova	So	Eliashiv	Foldvary	Luders	Rougier
AREA	95188.00	103061.00	4948.00	57767.00	53739.00	17250.00	913.20	700.70	7222.00	Not Fitted	Not Fitted	7117.00
SD	58.36	24.65	24.88	102.80	56.10	26.32	54.92	24.98	110.30			18.11
MEAN	-211.10	-94.91	-71.66	-338.70	-193.00	-88.31	-113.30	-56.42	-283.10			-58.26
AREA	22060000.00	19710000.00	359437.00	5195000.00	6121000.00	1634000.00	44765.00	77095.00	388226.00			937048.00
SD	942.80	280.90	179.70	756.10	478.30	193.90	480.60	427.40	760.00			199.90
MEAN	6956.00	2252.00	1084.00	5083.00	3378.00	1341.00	2076.00	2005.00	3986.00			1331.00
95% Confidence Intervals												
AREA	-94820000 to 9.501e+007	-62620000 to 6.282e+007	-4562000 to 4.572e+006	-22290000 to 2.241e+007	-26290000 to 2.639e+007	-5183000 to 5.217e+006	-98820 to 100650	-244600 to 246018	-838700 to 853166			-2975000 to 2.989e+006
SD	-3998 to 4115	-869.2 to 918.5	-2258 to 2308	-3151 to 3356	-2002 to 2114	-590.6 to 643.2	-1016 to 1126	-1335 to 1385	-1546 to 1766			-617.8 to 654.1
MEAN	-30140 to 29722	-7260 to 7070	-13840 to 13698	-22210 to 21533	-14730 to 14344	-4356 to 4180	-4738 to 4511	-6437 to 6324	-8969 to 8403			-4293 to 4176
Goodness of Fit												
Degrees of Freedom	2.0000	3.0000	1.0000	2.0000	2.0000	3.0000	10.0000	3.0000	12.0000			3.0000
R^2	0.9250	0.7414	0.9927	0.9851	0.9754	0.9095	0.6149	0.6352	0.9072			0.8241
Absolute Sum of Squares	0.0104	0.0692	0.0004	0.0014	0.0027	0.0179	0.0665	0.0404	0.0108			0.0391
Sy.x	0.0720	0.1519	0.0192	0.0268	0.0364	0.0772	0.0815	0.1160	0.0300			0.1141
Runs test												
Points above curve	3.0000	2.0000	2.0000	2.0000	2.0000	3.0000	6.0000	3.0000	6.0000			3.0000
Points below curve	2.0000	4.0000	2.0000	3.0000	3.0000	3.0000	7.0000	3.0000	9.0000			3.0000
Number of runs	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000	3.0000			3.0000
P value (runs test)	0.5000	0.4000	0.6667	0.5000	0.5000	0.3000	0.0076	0.3000	0.0030			0.3000
Deviation from Model	NSig	NSig	NSig	NSig	NSig	NSig	Significant	NSig	Significant			NSig

Table 40. Comparison of Curve Fits

	Jeha	Kelly	Spencer	McIntosh	Yoon	Jutila	Salanova	So	Eliashiv	Foldvary	Luders	Rougie
Model 1	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Not fitted	Not fitted	Gaussian
Model 2	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential
P value	Not Necessary	Not Necessary	Not Necessary	Not Necessary	Not Necessary	Not Necessary	Not Necessary	Not Necessary	Not Necessary	NA	NA	Not
Conclusion (alpha = 0.05)	Models have the same DF	Models have the same DF	Models have the same DF	Models have the same DF	Models have the same DF	Models have the same DF	Models have the same DF	Models have the same DF	Models have the same DF			Models have the same DF
Preferred model	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential	Exponential			Exponential

NA Not Applicable

Figure 11. Survival Functions for 12 Included Studies Fit Using Exponential Distribution



Meta-Analysis of Hazard Function Parameters

Effect Size Estimates

As discussed above, the hazard function for a survival curve with an exponential distribution is described by a single parameter, the constant hazard rate (λ). In order to model a summary survival curve, the hazard rate and its 95 percent confidence intervals for each included study was determined (Table 41). A hazard rate could not be determined for one of the 12 included studies (Luders et al.(134)) because too few data points were available for a curve to be fitted.

Table 41. Hazard Function Estimates and 95% Confidence Intervals for Included Studies

Reference	Jeha et al.	Kelly et al.	Spencer et al.	McIntosh et al.	Yoon et al.	Jutila et al.	Salanova et al.	So et al.	Eliashiv et al.	Foldvary et al.	Luders et al.	Rougier et al.
λ	0.29	0.72	0.30	0.09	0.17	0.44	1.02	2.12	0.16	1.54	NC	1.03
Lower 95 % CI	0.00	0.51	0.04	0.05	0.03	0.35	0.51	0.00	0.11	0.22	NC	0.39
Upper 95% CI	0.58	0.93	0.56	0.13	0.31	0.53	1.53	4.24	0.21	2.86	NC	1.67

NC=Not calculated

Heterogeneity Tests

The data presented in Table 41 were tested for heterogeneity using both the Q-test and I^2. Both tests found these data to be heterogeneous ($Q=137.27$, $P<0.0001$; $I^2=92.72$). Consequently, these data could not be combined in a fixed effects meta-analysis because they did not meet the assumption that data from the included studies were homogeneous.

Exploration of Heterogeneity

We explored heterogeneity using meta-regression as described in the *Methods* section of this evidence report. 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. Covariates considered in our analyses, which are presented in Table 42, were all identified *a priori* as potential contributors to heterogeneity. None of the covariates that could be assessed were found to independently have a significant impact on the risk rate, λ (Table 43). This should not be construed as meaning that the covariates listed below are unrelated to the risk rate. This is because the value of our analysis is limited by the fact that so little information pertaining to the covariates of interest were reported. For example, AED withdrawal following successful surgery is considered to be a potential risk factor for seizure recurrence.(127,130) Consequently, one would expect that differences among included studies in the proportion of seizure-free individuals who underwent AED withdrawal may be an important source of heterogeneity. Since few of the studies reported on the number of individuals who underwent drug withdrawal during follow up, it was not possible to determine the impact that this potentially influential covariate had on outcome.

Table 42. Covariates Considered in Univariate Meta-Regression Analyses

Reference	Year	Prospective?	Multicenter?	Quality score	% Male	Mn or Mdn age at surgery	Mn or Md age at onset of disease	Duration of disease at surgery	Mn or Mdn seizure frequency on study entry	Mn or Mdn IQ	% with abnormal MRI	% right sided resection	% who underwent AED withdrawal	% who experienced secondary generalized seizures	Mn or Mdn Followup time	Minimum seizure free period?	% with hippocampal sclerosis	% patients treated with temporal lobectomy?
Jeha et al.(128)	2006	No	No	6.1	NR	NR	NR	NR	NR	NR	NR	NR	20.8	NR	5.5 yrs	0 yr	66.8	100
Kelly et al.(129)	2005	No	No	4.3	NR	28.4 yrs	10.5 yrs	18.4 yrs	NR	NR	NR	54.2	NR	NR	29.9 yrs	0 yr	NR	100
Spencer et al.(126)	2005	Yes	Yes	8.2	NR	NR	NR	NR	NR	NR	84.9	NR	NR	77.1	2.4 yrs	2 yrs	66.5	87.6
McIntosh et al.(130)	2004	No	No	5.7	NR	NR	NR	NR	NR	NR	89.2	44.6	31%	51.2	9.6 yrs	0 yr	65.2	100
Yoon et al.(131)	2003	No	No	6.4	52.0	27.6	NR	16.3	NR	NR	NR	45.0	NR	NR	8.0 yrs	1 yr	54.0	84.0
Jutila et al.(132)	2002	No	No	6.4	NR	32.0	12.0	18.0	78 per yr	NR	65.0	67.9	NR	NR	5.4 yrs	0 yr	NR	100
Foldvary et al.(124)	2000	No	No	7.5	57.0	23.9	NR	12.9	12 per mo	NR	NR	43.0	18%	61.0	14.0 yrs	0 yrs	NR	100
Salanova et al.(123)	1999	No	No	7.5	NR	30.4	10.5	19.7	NR	NR	56.0	48.9	NR	NR	5.6 yrs	0 yrs	61.0	100
Eliashiv et al.(133)	1997	No	No	6.8	45.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	8.4 yrs	0 yrs	NR	100
So et al.(122)	1997	No	No	5.2	45.3	31.0	8.0	19.5	NR	NR	NR	NR	35%	NR	3.4 yrs	0 yrs	NR	100
Luders et al.*(134)	1994	No	No	5.9	54.3	NR	NR	NR	NR	NR	NR	NR	39.4	NR	NR	0 yrs	NR	84.5
Rougier et al.(135)	1992	No	No	5.9	59.0	29.0	NR	13.0	NR	NR	NR	NR	NR	NR	NR	0 yrs	NR	76.0
Covariate can be used in meta-regression analyses?		Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes

*Not included in meta-analyses so these data are not needed for meta-regression analyses.
NR=Not reported

Table 43. Findings of Univariate Meta-regression Analyses (unrestricted maximum likelihood models)

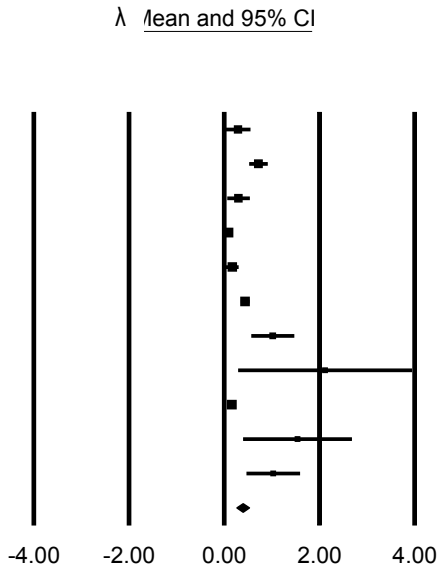
Covariate	Coefficient	95% CI	P=	Coefficient significant?	Residual	Model	Total	Tau²
Study level covariates								
Prospective?	0.18	-0.47 to 0.83	0.5849	No	14.55423	0.29845	14.85267	0.08569
Multicenter?	0.18	-0.47 to 0.83	0.5849	No	14.55423	0.29845	14.85267	0.08569
Min seizure free period	-0.15615	-0.45 to 0.14	0.30276	No	14.31580	1.06199	15.37778	0.08033
Study quality score	0.03	-0.18 to 0.23	0.79666	No	14.50846	0.06640	14.57486	0.05893
Patient level covariates								
% patients treated with temporal lobectomy?	-0.00	-0.03 to 0.02	0.88933	No	14.83790	0.01937	14.85726	0.08564

Pooling of Hazard Rate Data using a Random-Effects Model

Because we could not explain the observed heterogeneity across the hazard rates determined for each included study, we pooled these data using a random-effects model. Such a model allows the incorporation of heterogeneity into the summary estimate of the hazard rate and its confidence intervals. The result of this meta-analysis is presented in Figure 12. The random-effects summary hazard rate was found to be 0.39 (95 percent CI: 0.26 to 0.53).

Figure 12. Random Effects Meta-Analysis of Hazard Rate (λ) Data

Study name	Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Jeha	0.291	0.126	0.016	0.043	0.539	2.300	0.021
Kelly	0.720	0.092	0.008	0.540	0.900	7.850	0.000
Spencer	0.300	0.113	0.013	0.078	0.522	2.646	0.008
McIntosh	0.090	0.018	0.000	0.055	0.125	5.102	0.000
Yoon	0.170	0.061	0.004	0.050	0.290	2.788	0.005
Jutila	0.440	0.039	0.002	0.363	0.517	11.193	0.000
Salanova	1.020	0.223	0.050	0.583	1.457	4.579	0.000
So	2.120	0.926	0.857	0.305	3.935	2.290	0.022
Eliashiv	0.160	0.022	0.000	0.118	0.202	7.383	0.000
Foldvary	1.540	0.577	0.332	0.410	2.670	2.671	0.008
Rougier	1.030	0.280	0.078	0.482	1.578	3.682	0.000
	0.396	0.068	0.005	0.263	0.528	5.852	0.000



Construction of the Summary Survival Function

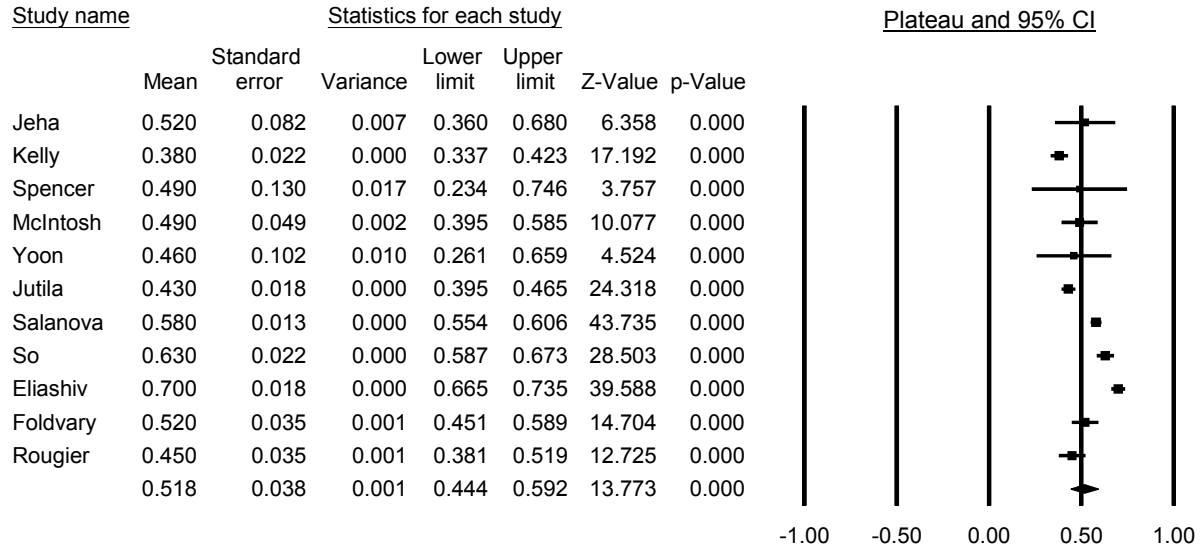
In order to simulate a summary survival curve from the random effects summary hazard rate estimate presented above, one must determine the constraints that apply. In this instance, it is clear that *S(t)* will not decay to zero as t approaches infinity. Rather, for each included study, *S(t)* reaches a plateau (Figure 11) at some value >0. Because the plateau differs from study to study (Table 44) it is necessary to determine a summary estimate of *S(t)* for each study at its plateau

and then pool these data using random-effects meta-analysis in order to obtain an "average" plateau. The result of this analysis is presented in Figure 13.

Table 44. Plateau and 95% CI for Included Studies

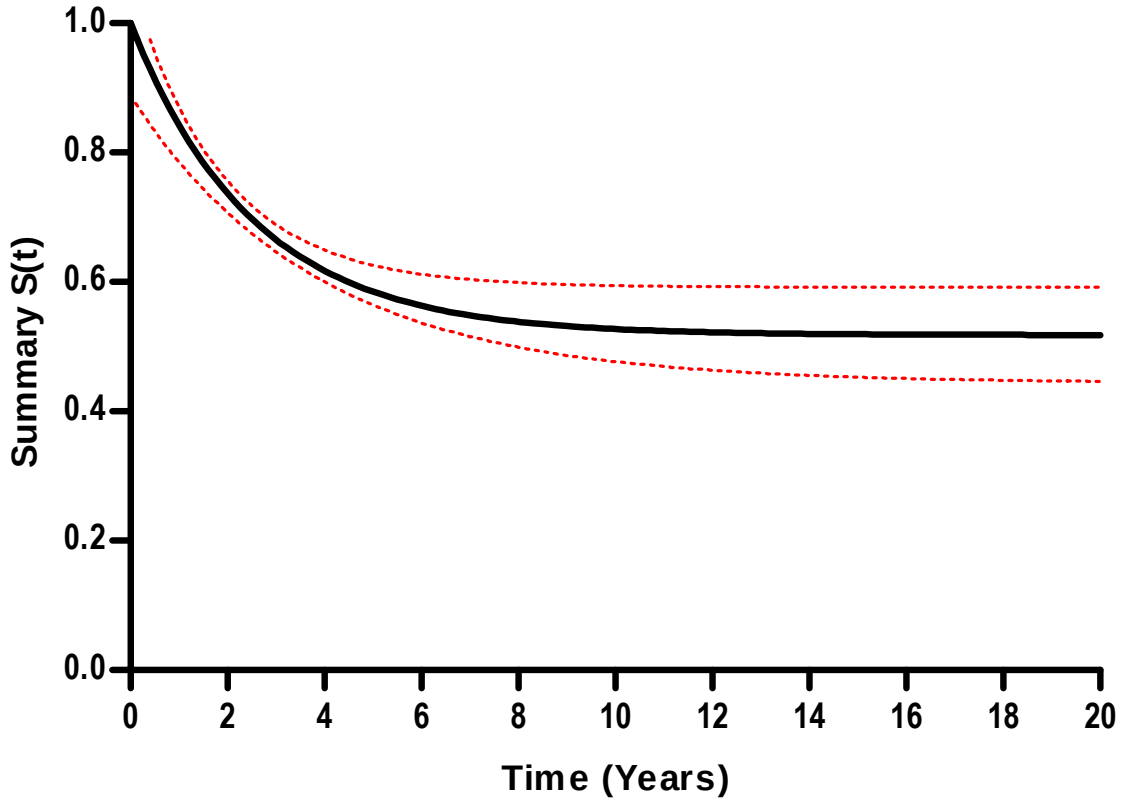
Reference	Jeha et al.	Kelly et al.	Spencer et al.	McIntosh et al.	Yoon et al.	Jutila et al.	Salanova et al.	So et al.	Eliashiv et al.	Foldvary et al.	Luders et al.	Rougier et al.
Plateau	0.52	0.38	0.49	0.49	0.46	0.43	0.58	0.63	0.70	0.52	NC	0.45
Lower 95 % CI	0.34	0.33	0.20	0.38	0.23	0.39	0.55	0.58	0.66	0.44	NC	0.37
Upper 95% CI	0.71	0.43	0.79	0.60	0.69	0.47	0.61	0.68	0.74	0.60	NC	0.53

Figure 13. Determination of Lower Constraint (Plateau) for Simulated Summary Survival Curve



Having determined a summary estimate for the plateau and the hazard rate, we next generated a summary survival curve. This simulated summary survival curve is presented in Figure 14.

Figure 14. Summary *S(t)* and 95% Confidence Interval



Note that time is from time an individual meets the criteria for seizure free (usually 1 year without a seizure)

Probability of Seizure Recurrence in Next Year given Prespecified Seizure Free Period

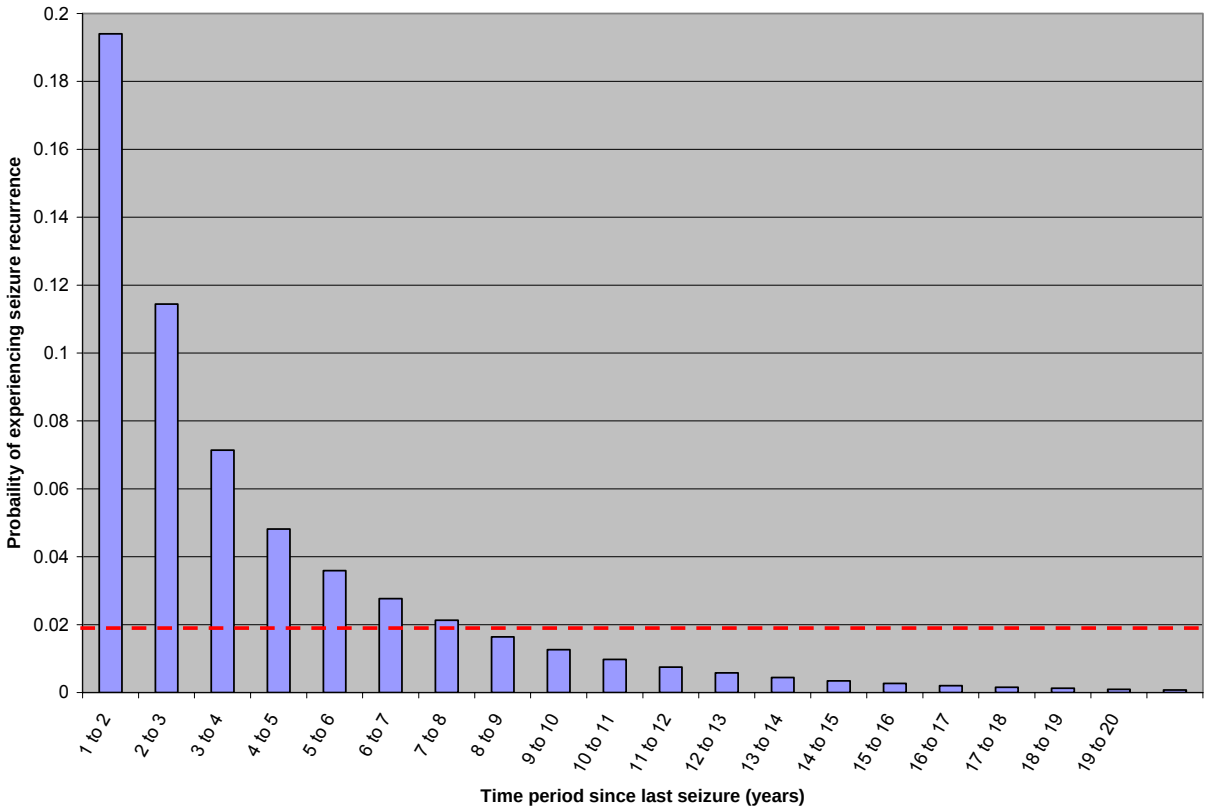
The Austroads guidelines (see *Background* section) suggest that an annual seizure risk of 20 percent–50 percent for private license holders and 1 percent–2 percent for commercial drivers are acceptable levels for an individual to drive. Consequently, we used the summary survival curve constructed above (Figure 14) 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 (Table 45). These data which are shown graphically in Figure 15 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.

Table 45. Conservative Estimate of Probability for Experiencing Seizure Recurrence in Year following a Seizure Free Period >1 year

Seizure free period (Yrs)	Time Period (Yrs)	S(t1)-S(t2)/dt (Lower CL)	S(t1)-S(t2)/dt (Curve)	S(t1)-S(t2)/dt (Upper CL)	Conservative Estimate
1	1 to 2	0.101995	0.156961	0.194033	0.194033
2	2 to 3	0.078565	0.105848	0.114437	0.114437
3	3 to 4	0.060517	0.071379	0.067493	0.071379

Seizure free period (Yrs)	Time Period (Yrs)	S(t1)-S(t2)/dt (Lower CL)	S(t1)-S(t2)/dt (Curve)	S(t1)-S(t2)/dt (Upper CL)	Conservative Estimate
4	4 to 5	0.046615	0.048135	0.039806	0.048135
5	5 to 6	0.035907	0.032460	0.023477	0.035907
6	6 to 7	0.027658	0.021889	0.013846	0.027658
7	7 to 8	0.021305	0.014761	0.008166	0.021305
8	8 to 9	0.016411	0.009954	0.004816	0.016411
9	9 to 10	0.012641	0.006713	0.002841	0.012641
10	10 to 11	0.009737	0.004527	0.001675	0.009737
11	11 to 12	0.007500	0.003053	0.000988	0.007500
12	12 to 13	0.005777	0.002059	0.000583	0.005777
13	13 to 14	0.004450	0.001388	0.000344	0.004450
14	14 to 15	0.003428	0.000936	0.000203	0.003428
15	15 to 16	0.002640	0.000631	0.000120	0.002640
16	16 to 17	0.002034	0.000426	0.000070	0.002034
17	17 to 18	0.001567	0.000287	0.000042	0.001567
18	18 to 19	0.001207	0.000194	0.000024	0.001207
19	19 to 20	0.000930	0.000131	0.000015	0.000930
20	20 to 21	0.000716	0.000088	0.000008	0.000716

Figure 15. Annual Risk for Experiencing Seizure Recurrence Following a Seizure Free Period of >1 year



This figure shows that the annual seizure recurrence risk falls below the acceptable risk for commercial motor vehicle drivers in Australia after a seizure free period of 8 years. If stricter criteria were used, such as a 1% seizure recurrence risk, one would not permit an individual with epilepsy to drive a commercial vehicle until they have been seizure free following surgery for at least 10 years.

Other Risk Factors for Seizure Recurrence

Although there is an inverse relationship between time since surgery and the probability for seizure recurrence, a number of further "modifying" factors have also been identified. These factors will have an impact on the accuracy of the seizure recurrence probabilities presented above. Additional factors that have been assessed and found to be predictive of seizure recurrence among "seizure-free" individuals are seizure presented in Table 46. The reader should note that there is little agreement at this time as to which factors comprise the best predictors of seizure recurrence among individuals who were considered seizure free following surgery.

Table 46. Risk Factors for Seizure Recurrence following Surgery

Reference	Year	Type of surgery	Definition of Seizure Free	Method used to identify risk factors	Risk factors considered	Significant Risk Factors
Spencer et al.(126)	2005	Temporal lobectomy or other neocortical resections	Seizure free with or without aura ≥2 yrs	Bivariate analyses were performed with Chi-square tests and tests for trend when appropriate. In addition, proportional hazards analysis used to estimate bivariate rate ratios (RR) for each factor with respect to both of the outcomes, 2-year remission and relapse after 2-year remission. For multivariate analysis, authors used a proportional hazards model.	*Seizure variables* • Classification • Frequency • Severity *Chronologic variables* • Duration of epilepsy • Age at onset of epilepsy • Age at study entry *Demographic variables* • Sex • Race • Cognitive function • Education • Employment *Other variables* • MRI with focal abnormal features unilateral or bilateral hippocampal atrophy on qualitative interpretation, with or without signal change • Ictal and interictal EEG localization from scalp and intracranial recordings *Postoperative variables* • Results of pathology report • Interval to seizure remission (counted from day of hospital discharge) • Presence of auras in post operative seizure-free patients	• Interval to seizure remission (Individuals who entered remission slowest more likely to relapse)
Kim et al.(127)	2005	Temporal lobectomy	Seizure-free with no auras ≥1 yr	Comparison of recurrence rate among those who underwent AED withdrawal (20/60) and those who did not (1/6)	• AED withdrawal* • Duration on AED from onset of a seizure-free state to time of withdrawal • Immediate or delayed remission	• AED withdrawal* • Duration on AED from onset of a seizure-free state to time of withdrawal

Reference	Year	Type of surgery	Definition of Seizure Free	Method used to identify risk factors	Risk factors considered	Significant Risk Factors
McIntosh et al.(130)	2004	Temporal lobectomy	Seizure free with or without aura≥2 yrs	Univariate and Multivariate Cox proportional hazards regression modeling	• AED withdrawal* • Pathology • Age at disease onset • Duration of disease • Age at surgery • Preoperative generalized seizure	• No risk factors significant
Burneo et al.(136)	2005	Temporal lobectomy	Engel I at 1 year	Univariate and Multivariate logistic regression	• Race • Age at surgery • Duration of disease • History of febrile seizures • Lateralization of foci • Handedness	• Left lateralization of seizure foci • African-American Race
Stavem et al.(137)	2004	Temporal lobectomy	Engel I, ≥2 yrs	Logistic regression analysis	• Gender • Age at surgery • Age at onset of seizures • Duration of disease • Etiology • Generalized vs not generalized seizures • Seizure frequency Intelligence quotient • Ictal EEG findings • MRI findings • SPECT findings • Side of resection • Extent of the resection	• Focal pathology in preoperative MRI • Extent hippocampal resection
Yoon et al.(131)	2003	Temporal lobectomy	Seizure free, ≥1 yr	Univariate and Multivariate Cox proportional hazards regression modeling. Univariate and Multivariate logistic regression	• Gender • Age at surgery • Age at onset of seizures • Duration of disease • Etiology • Side of resection	Univariate • Age at surgery • Duration of disease • Pathology Multivariate • Duration of disease • Normal pathology
Jutila et al.(132)	2002	Temporal Lobectomy	Seizure free	Logistic regression analysis	• History of (complex) febrile seizures • Age at onset of disease • Duration of disease • Etiology of epilepsy (MRI)	• Onset of epilepsy before the age of five years • Hippocampal atrophy with or without temporal cortical atrophy on qualitative MRI • Other unilateral structural lesions of the

Reference	Year	Type of surgery	Definition of Seizure Free	Method used to identify risk factors	Risk factors considered	Significant Risk Factors
					• Preoperative seizure frequency • Seizure type predominance • Type of operation	temporal lobe on qualitative MRI • Focal seizures with ictal impairment of consciousness • Focal ictal EEG as a predominant seizure type
Salanova et al.(138)	2002	Temporal lobectomy	Engel I, 1 yr	Comparison of group of seizure free individuals and individuals with seizure recurrence	• Age at surgery • Duration of disease • Side of resection	• No risk factors significant
Killpatrick et al.(139)	1999	Temporal lobectomy	Engel I	Comparison of group of seizure free individuals and individuals with seizure recurrence Significant differences in factors across two groups tested using Mann-Whitney U-test	• % patients with a history of febrile seizures • Mean age at febrile convulsions • % women • % left temporal lobectomy • Mean age of onset of non-febrile seizures • Mean age at surgery • Duration of epilepsy • Number of patients with greater than weekly seizures • Number of pts with history of secondary generalized seizures • Frequency of secondary generalized seizures in previous 5 years	• No risk factors significant
Eliashiv et al.(133)	1997	Temporal lobectomy	Engel I	Kaplan Meir curves for subgroups compared using log-rank test	• Age at surgery • Duration of disease • Lesion pathology • Psychological adjustment • Risk factors for epilepsy	• Lesion pathology • Duration of disease • Psychological adjustment

Section Summary

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).**

12 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 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 (see Background section) 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.

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?

Introduction

Unprovoked seizures are defined as seizures that occur without an identified proximate precipitant.(140) They are further classified into remote symptomatic seizures (associated with a known neurological injury or syndrome, but without the *acute* precipitating event or insult which initiates the seizure activity) or idiopathic/cryptogenic seizures(the cause does not appear to be related to a recognized insult to the central nervous system or other condition).(141,142)

Approximately 5 percent of the population will experience at least one unprovoked seizure during their lifetime.(143,144) The risk of experiencing a first unprovoked seizure appears to increase with age: Kotsopoulos et al. estimated that the annual incidence of unprovoked seizures was 25 per 100,000 people among those aged 24-44; 51 per 100,000 people among those aged 45-64; and 120 per 100,000 people among those aged 65 or older.(145) Some individuals who have an unprovoked first seizure will eventually go on to have additional seizures and be diagnosed with epilepsy, a chronic condition characterized by multiple recurrent unprovoked seizures.(18,144)

Risk Factors for Seizure Recurrence and Driver Safety

The risk of seizure recurrence poses a potential danger, particularly in individuals involved in certain occupations like driving and operating dangerous machinery.(146) Therefore, it is important to have an estimate of the risk of relapse and to identify individuals who are at higher risk of recurrence. Reported risk factors for seizure recurrence include the following: an underlying neurological abnormality (remote symptomatic etiology), presence of epileptiform activity on EEG, focal neurological findings, tumors or other progressive lesions and family history of seizure.(141,147)

Rationale for Key Question

Current FMCSA recommendations suggest that an individual who has had a single unprovoked seizure without seizure recurrence for at least 5 years and who is not taking an AED may be considered fit to drive a CMV. This recommendation takes into account the contention that the

annual risk for seizure recurrence is acceptably low after this period of time in this specific population. In this section we identify studies that have directly measured the time-to-seizure recurrence in groups of individuals who have experienced a single unprovoked seizure in order to quantify the relationship between seizure-free period and seizure recurrence likelihood.

Identification of Evidence Base

The identification of the evidence base for Key Question 4 is summarized in Figure 16. Our searches (Appendix A) identified a total of 197 articles that appeared to be relevant to this key question. Following application of the retrieval criteria (Appendix B) for this question, 43 full-length articles were retrieved and read in full. Of these 43 articles, four met the inclusion criteria (Appendix C) for Key Question 4. Table D-4 of Appendix D lists the 39 articles that were retrieved but then excluded and provides rationale for their exclusion. Table 30 lists the four articles that met the inclusion criteria for Key Question 4.

Figure 16. Development of Evidence Base for Key Question 4

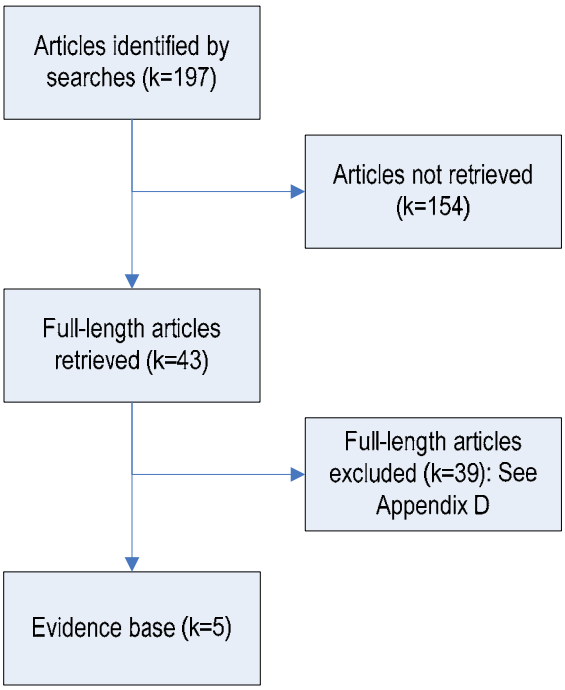


Table 47. Evidence Base for Key Question 4

Reference	Year	Study Location	Country
Kollar et al.(148)	2006	Comenius University	Slovak Republic
Gilad et al.(143)	1996	Edith Wolfson Medical Center	Israel
van Donselaar et al.(149)	1991	University Hospital, Rotterdam	The Netherlands
Hopkins et al.(144)	1988	St. Bartholomew's Hospital, London	United Kingdom

Evidence Base

This subsection provides a brief description of the key attributes of the four studies that comprise the evidence base for this key question. Here we discuss pertinent information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of commercial vehicles.

Characteristics of Included Studies

The primary characteristics of the four included studies that address Key Question 4 are presented in Table 48. The four studies were published between 1988 and 2006, and enrolled a total of 777 individuals. Three studies were prospective. The remaining study was both prospective and retrospective. Two studies began monitoring patients very soon after the single seizure. In the remaining two studies, some time had elapsed (e.g., 10 days) between the single seizure and the start of patient monitoring. The maximum length of follow-up ranged from two to seven years.

Each study attempted to verify two critical aspects: 1) that this was the patients first-ever seizure, and 2) that the seizure was unprovoked. All four studies stated explicitly that the intent was to assess the risk of recurrence in patients who had a single unprovoked single seizure. Details of each study's verification methods appear in Table 49. In three studies (Glad et al., van Donselaar et al. and Hopkins et al), the diagnosis was made based on the medical history, the observations of eyewitnesses, the neurological examination and the findings from the family history. A complete description of the first seizure was provided and previous events were explored. In Kollar et al., information was collected from clinical documentation and completed patient histories. Blood tests were performed to screen for medical disorders that may be linked to seizures in three of the included studies. Additional diagnostic procedures used to support the clinical examination included EEG, CT and MRI: an EEG was obtained for most of the patients in all 4 included studies, CT scanning was performed in three of the studies, and MRI was mentioned in only one study.(143)

Table 48. Key Study Design Characteristics of Studies that Address Key Question 4

Reference	Year	Design	Population source	N=	Time between seizure and referral	Follow-up time
Kollar et al.(148)	2006	Prospective and retrospective	University hospital	30	None; study reported individual ages at time of seizure, and also seizure recurrences from that time point	3 to 7 years
Gilad et al.(143)	1996	Prospective	Outpatient clinic	87	Less than 24 hours	Up to 36 months or until recurrence of 2d seizure
Van Donselaar et al.(150)	1991	Prospective	University and general hospitals	165	Less than 24 hours: 51% 1-14 days: 35% 14-90 days: 14%	1 to 2 years
Hopkins et al.(144)	1988	Prospective	Specialty clinical referrals	408	Less than one week: 25% 1 wk-1 mo: 25% 1 mo-2 mo: 26% 2 mo-?: 24%	Up to 4 years

Table 49. Case Ascertainment Methods in Studies that Address Key Question 4

Reference	Year	Single seizure	Unprovoked seizure
Kollar et al.(148)	2006	Information collected from clinical documentation and from completely filled out forms of patient history.	Investigators evaluated patient history of febrile seizures, family history of epilepsy, neurological status, type of convulsion, EEG findings
Gilad et al.(143)	1996	A diagnostic was based on the description of the reported attack by observers and on the findings from the family history, and was classified clinically according the International Classification of Epilepsy (1989). Exclusion criteria: • Patients with history of partial seizures • Patients presenting with status epilepticus	All patients examined by 3 neurologists. Detailed family history was evaluated. Biochemical analysis, echocardiography, EEG, CT and MRI were performed for every patient. Exclusion criteria: • Seizure induced by alcohol or other drugs or toxic substances; including metabolic disorder • Progressive neurological disease • New or old infarction of the brain • Intracerebral bleeding • Brain tumors • Vascular malformations confirmed by in medical history or neurological imaging
Van Donselaar et al.(150)	1991	The diagnosis was based on the description of the episode according to prespecified diagnostic criteria, the medical history , and the neurological examination. Exclusion criteria: • Patients who had seizures other than febrile convulsion in the past • Patients presenting with status epilepticus. • Patients that may have experienced a seizure lasting longer than 30 minutes.	All patients evaluated by 3 neurologists before admission. Patients were admitted if it appeared to be no clinical cause for seizure. Patients with seizures that may have been induced by sleep deprivation or stress were included. (Patients who had experienced extreme conditions such as not sleeping for several days were excluded). Blood samples were obtained for all patients and CT was done on 162 patients Standard EEG was done on 151 patients. All EEGs were read by one neurologist who had no access to the clinical information (blinded); rated as normal, showing epileptic discharges or showing other abnormalities.
Hopkins et al.(144)	1988	Neurologist obtained descriptions of first seizure at the initial neurological consultation. Exclusion criteria: • Medical history revealed first seizure was not the first (absence in childhood) • Patients who had more than one seizure in 24 hours • Patients who had their second seizure after referral but before attending the neurological outpatient clinic	Neurologist obtained relevant medical information such as family history of febrile convulsions or seizures, history of previous head injury. EEG , CT, Hematological and biochemical screening tests were performed. EEGs were coded by clinical neurophysiologist at referring center and sometimes by the authors. Anoxic seizures were excluded. Investigators made no attempt to exclude seizures provoked by alcohol or its withdrawal.

Quality of Included Studies

The findings of our assessment of the quality of these studies are presented in Table 50. Our assessment of the quality of the studies that comprise the present evidence base found the quality of one study to be moderate, and three studies to be low. Therefore, the overall quality of the evidence base was low (Median Quality Score: 6.72, Quality = Low). The primary reasons for the low quality were: less than 85 percent of patients completing the study to the longest time point (three studies); patient monitoring began more the one week after the single seizure (two studies); only one study reported that patients were monitored proactively for seizure recurrence; no report regarding whether consecutive patients were enrolled (two studies); no report regarding whether the inclusion/exclusion criteria were established a priori (two studies); and lack of reporting of funding source (two studies).

Table 50. Quality of the Studies that Address Key Question 4

Reference	Year	Quality Scale Used	Quality Score	Quality
Kollar et al.(148)	2006	ECRI Quality Assessment Instrument X: Case-Series (time-to-event)	5.6	Low
Gilad et al.(143)	1996	ECRI Quality Assessment Instrument X: Case-Series (time-to-event)	8.3	Moderate
Van Donselaar et al.(150)	1991	ECRI Quality Assessment Instrument X: Case-Series (time-to-event)	6.1	Low
Hopkins et al.(144)	1988	ECRI Quality Assessment Instrument X: Case-Series (time-to-event)	6.7	Low

Generalizability of Evidence to Target Population

The purpose of this subsection is to provide details of the extent to which the individuals enrolled in the studies that address Key Question 4 are similar to CMV drivers in the United States. Important characteristics of the individuals included in the studies that address Key Question 4 are presented in Table 51.

The generalizability of the individuals enrolled in the four included studies to CMV drivers is unclear. None of the studies included information about the occupation or the driving experience of the participants, making it difficult to generalize on the basis of employment or driving exposure. Other factors that may limit the generalizability of the findings of the four studies to the target population include the following: 1) The proportion of women in the included studies is higher than the prevalence of female CMV drivers; and 2) Some of the individuals enrolled in these studies were very young. However, CMV drivers in the United States tend to be older (over 40 years of age) and often have a number of medical conditions.

Table 51. Individuals in Studies that Address Key Question 4

Reference	Year	Inclusion criteria	Exclusion criteria	N=	Age (years) mean ± SD	Seizure type	Etiology	% treated	% Male	% CMV drivers	Driving exposure	Generalizability to CMV population
Kollar et al.(148)	2006	Patients dispensary of the 1st Department of Neurology, Comenius University and Faculty hospital in Slovakia	NR	30	39 Rng: 19-81	Generalized: 50% Partial: 50%	Idiopathic/ Cryptogenic: 27% Late symptomatic: 73%	47%	53%	NR	NR	Unknown
Gilad et al.(143)	1996	Age: between 18 and 50 years, patients seen in outpatient clinic between 1985 and 1990 that experienced a single epileptic attack of the generalized tonic-clonic type, and presentation at the hospital within 24 hours after the attack.	Partial seizures, Seizure induced by alcohol or other drugs or by metabolic disorders Status epilepticus, progressive neurological disease, new and old infraction of the brain, intracerebral bleeding, brain tumor, vascular malformation	87	Treated group: 30.12 ±1.3 Untreated group: 32± 2.5	Generalized tonic-clonic: 100%	NR	52%	48%	NR	NR	Unknown
Van Donselaar et al.(150)	1991	All patients ≥ 15 years with a presumed idiopathic untreated first seizure referred to the hospital between 1986 and 1988. Patients with seizures that may have been induced by sleep deprivation or stress were included	Patients who had had a seizure other than febrile convulsions in the past, patients presenting with a status epilepticus, pts experiencing extreme conditions such as not sleeping for several days.	165	38 (range 15-85)	Majority: generalized Partial: 3 pts	Idiopathic	15%	59%	NR	NR	Unknown
Hopkins et al.(144)	1988	All patients (inpatients, outpatients, private patients) > 16 years referred with a first seizure	History of previous seizures, diagnosed neurological disease, more than one seizure in 24h, anoxic seizures	408	NR	Generalized tonic-clonic: 97.5% Partial: 2.2 % Other: 0.3%	Idiopathic	15%	NR	NR	NR	Unknown

NR=not reported

Findings

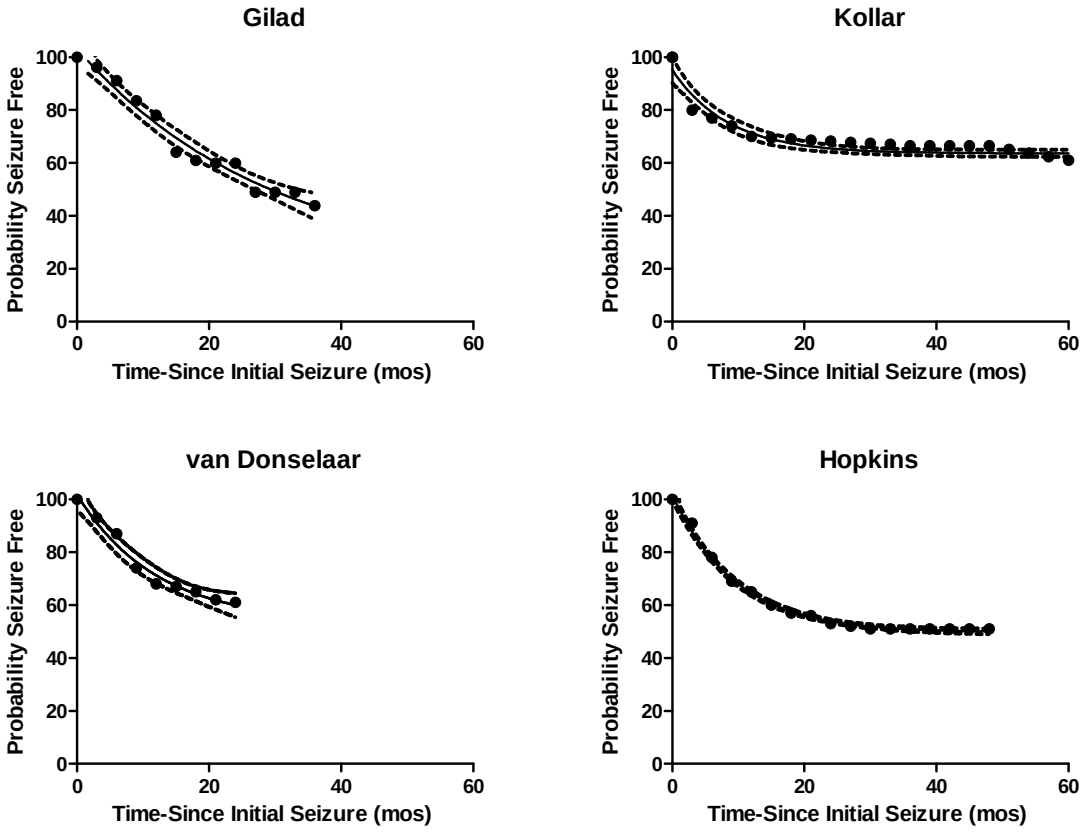
All four studies reported a survival curve or provided sufficient information for calculation of the survival curve. Relevant data extracted from these studies is presented in Table 52.

Table 52. Time-to-Seizure Recurrence Following a Single Unprovoked Seizure

Reference	Year	Event	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months	54 months	60 months
Kollar et al.(148)	2006	1.00	77.00	70.00	69.16	68.32	67.48	66.50	66.50	66.50	63.75	61
Gilad et al.(143)	1996	1.00	91.23	78.08	60.93	59.98	48.93	43.88	-	-	-	-
Van Donselaar et al.(150)	1991	1.00	87.00	68.00	65.00	62.00	-	-	-	-	-	-
Hopkins et al.(144)	1988	1.00	78.00	65.00	57.00	56.00	51.00	51.00	51.00	51	-	-

Using the methodology described in the previous section, we fit nonlinear models to the data extracted from each study. As was the case above, time-to-seizure recurrence data from each study was best fit using a non-linear regression model in which the underlying probability distribution was exponential. These resulting curves are presented in Figure 17.

Figure 17. Fitted Survival Curve Data for Key Question 4



Meta-Analysis of Hazard Function Parameters

Effect Size Estimates

In order to model a summary survival curve, the hazard rate and its 95% confidence intervals for each included study was determined (Table 53).

Table 53. Hazard Function Estimates and 95% Confidence Intervals for Included Studies

	Kollar et al.(148)	Gilad et al.(143)	Van Donselaar et al.(150)	Hopkins et al.(144)
λ	0.117800	0.034070	0.08304	0.104700
Lower 95 % CI	0.081700	0.009975	0.02987	0.093970
Upper 95% CI	0.154000	0.058170	0.13620	0.115500

NC=Not calculated

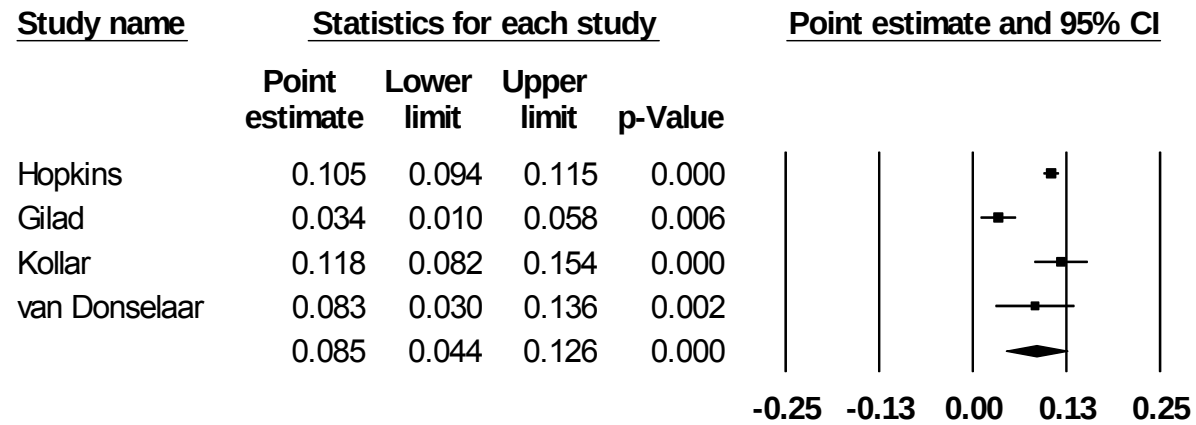
Heterogeneity Tests

The data presented in Table 53 were tested for heterogeneity using both the Q-test and I^2. Both tests found these data to be heterogeneous ($Q=29.38$, $P<0.0001$; $I^2=89.79$). Consequently, these data could not be combined in a fixed-effects meta-analysis because they did not meet the assumption that data from the included studies were homogeneous.

Heterogeneity Tests

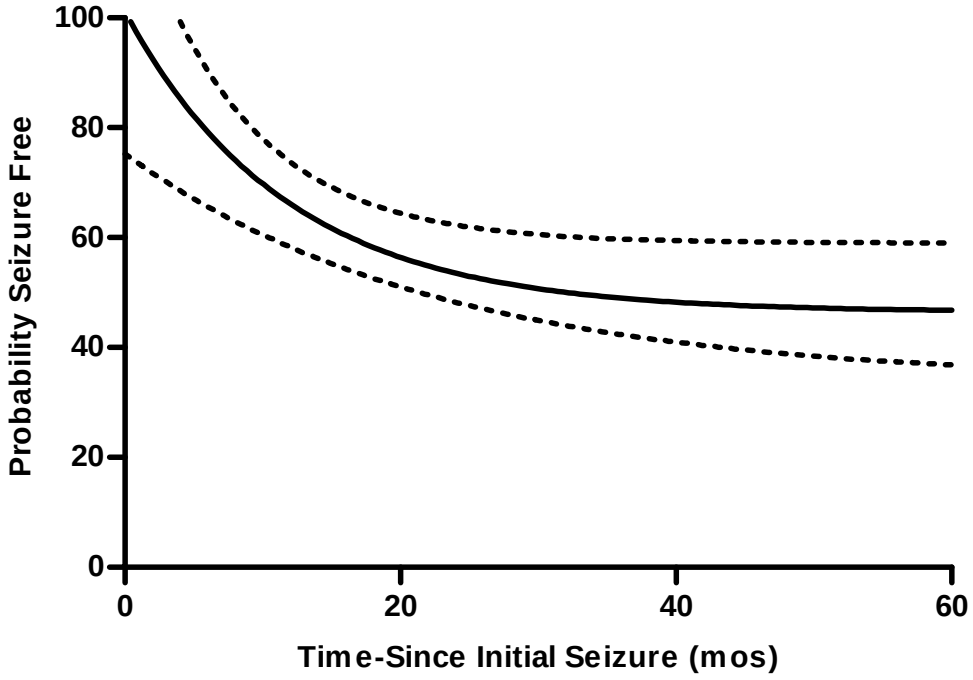
Due to the small evidence base, we did not attempt to explain this heterogeneity via meta-regression. Instead, we pooled the hazard rate data using a random-effects model meta-analysis (Figure 18) and constructed a summary time-to-event curve using the methodology described above. This curve, which utilized a hazard rate estimate of 0.085 (95% CI: 0.044 to 0.126), is presented in Figure 19.

Figure 18. Meta-Analysis of Hazard Rate Constant Data from Non-Linear Curve Fits



Having determined a summary estimate for the plateau and the hazard rate, we next generated a summary survival curve. This simulated summary survival curve is presented in Figure 19.

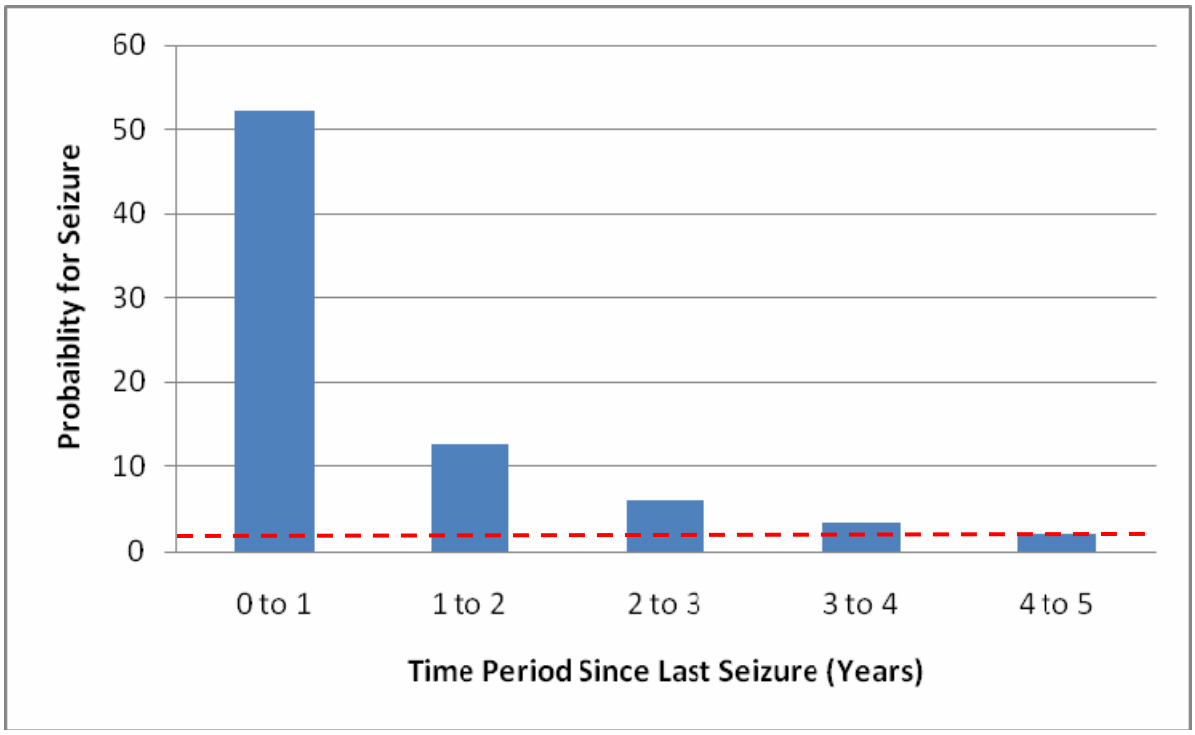
Figure 19. Summary Survival Curve for Key Question 4



Probability of Seizure Recurrence in Next Year given Prespecified Seizure Free Period

As stated in the previous section, the Austroads guidelines suggest that an annual seizure risk of 1 percent–2 percent is acceptable to allow an individual to drive a commercial motor vehicle. Consequently, we used the summary survival curve constructed above (Figure 19) to determine a conservative estimate of the likelihood that an individual who has experienced a single unprovoked seizure will experience seizure recurrence within the following year given that they have been seizure free for a specified period of time. These data, which are shown graphically in Figure 20, suggest that individuals who have been seizure free for at least four years have an annual risk for seizure recurrence risk of ≤2 percent. A paucity of longer-term follow up data precludes one from determining the seizure free period required before the annual risk for seizure recurrence is ≤1 percent.

Figure 20. Annual Risk for Experiencing Seizure Recurrence Following a Given Seizure Free Period



While Figure 20 provides some preliminary estimates of the risk for seizure recurrence following a specific period of seizure freedom, we caution the reader that we consider these estimates to be extremely unstable. Our lack of confidence in the stability of the estimates provided stems primarily from the fact that the evidence base from which our model was developed is particularly small and follow up times for which seizure recurrence data was reported was short.

Other Potential Risk Factors For Seizure Recurrence

Other factors may also be associated with increased recurrence risk (Table 54). Three associations were observed in more than one study:

- No immediate use of AEDs. The use of AEDs immediately after the single seizure is associated with a lower recurrence risk.
- Nighttime seizure. If the single seizure occurred at night during sleep, recurrence risk is higher than with a daytime first seizure. One possible explanation is that patients with seizures occurring during sleep may have had previous unrecognized seizures, which might cause a greater likelihood of recurrence.(147)
- Time between seizure and referral to specialist. A greater lag time has been found to predict a lesser risk of seizure recurrence.

Results for other factors have been mixed (age, EEG, AEDs, time of day). Some factors have consistently shown no association with recurrence risk (family history, sex, and seizure type). All other factors in the table were investigated in only one of the four studies.

Table 54. Other Factors that May Increase Seizure Recurrence Risk

	Kollar(148)	Gilad(143)	Van Donselaar(150)	Hopkins(144)
General individual characteristics				
Age	No association	NR	Younger age	No association
Family history	No association	NR	No association	No association
Sex	No association	NR	No association	NR
Seizure-related characteristics				
Febrile seizures	No association	NR	NR	NR
Seizure type	No association	NR	NR	No association
Structural cerebral lesion	No association	NR	NR	NR
Tongue bite	NR	NR	Positive history	NR
Diagnostic test results				
Abnormal neurological exam	No association	NR	NR	NR
CT	NR	NR	NR	Tumor on CT
EEG	No association	No association	Epileptic discharges on EEG	No association
Other factors				
Anti-epileptic drugs (AEDs)	No immediate treatment	No immediate treatment	NR	No association
Provocative circumstances	NR	NR	No association	NR
Time of day	No association	NR	Nighttime seizures	Nighttime seizures
Time between seizure and referral to specialist	NR	NR	>1 day but <2 weeks between seizure and referral	<8 weeks between seizure and referral

NR – Study did not investigate the association between this factor and seizure recurrence
Note: If a study reported a statistically significant association, then the table entry describes the direction of association. For example, the entry "Younger age" means that younger individuals had a greater risk of seizure recurrence than other individuals.

Section Summary

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?

Introduction

The standard of care for most individuals with epilepsy is medication therapy aimed at reducing or eliminating the frequency of seizures. Because individuals with the disorder may be required to use AEDs for extended periods of time, compliance (and resulting seizure control) is a particularly important issue to address. Estimates of medication compliance among individuals with epilepsy range from a low of 20 percent to a high of 75 percent.(151,151) In addition to safety concerns associated with reduced seizure control, monetary costs must be considered. Garnett reports that the average cost of treatment for an uncontrolled individual with epilepsy who has frequent seizures is $138,602 versus $4,272 for a person with controlled disease (in 1990 dollars).(152)

Noncompliance with AED treatment comes in many forms, including: not taking the correct dosage (too much or too little); not taking medication at the correct time of day; not taking the medication for the entire prescribed period; self-regulating the medication or taking it only when an individual thinks it is needed; or taking other medications that have been proscribed by the treating physician because they may interact with the AED.(151)

Studying medication compliance is not a straightforward endeavor, in part because definitions of compliance and non-compliance vary widely in the literature. Some researchers treat compliance

and non-compliance as two discreet categories, while others examine compliance and non-compliance as a continuum Another approach utilized is the examination of outside influences on compliance such as limited access to medication.(151) Garnett(152) has recommended using the term adherence over compliance, suggesting that the former term is more inclusive by making the individual with epilepsy more visible in the decision-making process. The latter term, according to Garnett invokes images of the physician as parent, with the patient/child merely following orders.

Reasons for non-compliance

There are many reasons for medication non-compliance among epileptic patients. Some of these issues are addressed in this section of the report.

Cost

Anti-epileptic medications are costly, which can be prohibitive for individuals with a limited income, who are self-employed, or who lack health insurance.(153-156)

Difficulty following dosage regimen/frequent dosing schedule

Anti-epileptic therapy regimens can be complicated to follow: medications may need to be taken several times a day; medications may need to be scheduled to avoid the potential for drug interactions; use of other medications (whether prescribed or over the counter) must also be carefully monitored to avoid drug interaction. Noncompliance due to memory impairment associated with age(155) or the disorder is not unknown: Garnett reports that even among those individuals who want to be compliant, non-compliance may result from forgetfulness brought on by their uncontrolled seizures.(152)

Adherence to AED use is inversely associated with the number of times a day an individual has to take the drug.(152,154) Garnett suggests physicians use “adherence cues” such as reminding patients to take morning medication when they brush their teeth or purchasing a daily pill holder to increase compliance.(152)

Side Effects

Both the ‘traditional’ (pre-1993) and ‘new’ AEDs have side effects: sedation; ataxia (partial or total loss of coordinated movement) and nausea are common AED associated adverse events, along with cosmetic effects such as weight gain, hirsutism and gingival hyperplasia.(151)

Among older adults with epilepsy who participated in a quality of life study, 64 percent reported that medication side effects reduced their quality of life.(153) For more information on common side effects of AEDs, see the “*Background*” section above.

Poor patient education/comprehension of the disease

Long et al. found that 30 percent of individuals who participated in disorder knowledge study believed epilepsy was a mental disorder or a contagious disease.(157) Garnett found that some individuals who were currently seizure free believe that medication was no longer necessary.(152)

Denial of Illness

As with any disorder, some individuals with epilepsy have been demonstrated to be in denial about their medical condition.(152)

Lack of Support Systems

Factors such as a good support system in the home and feeling a part of the decision-making process in their treatment plan have been found in the literature to be associated with increased compliance in individuals with epilepsy.(151,152,154)

Incidence and Prevalence of Patients on AEDS in the United States

For a detailed discussion on how many individuals with epilepsy in the United States are currently prescribed at least one AED, see the "*Background*" section above..

Methods for measuring compliance and non-compliance

Compliance has been assessed using a variety of methods; both non-invasive and invasive. Below we consider several of these methods and explain why we chose to consider only those studies that measured AED treatment compliance using serum drug level testing.

Non-invasive methods for measuring AED treatment compliance

Researchers measure medication compliance and non-compliance in a number of ways. The simplest and least expensive method is self-report, which is usually ascertained by interview or questionnaire. While some researchers have found that there is agreement between self-reported and other more objective measures of compliance, self-reports are considered unreliable because evidence suggests that some patients tend to overestimate their degree of compliance.(154,156,158,159) For example, in a systematic review of medication adherence for a whole spectrum of disorders, Krueger et al. found that self-report overestimated compliance by between 130 percent-200 percent when compared with more objective biochemical measures and pill counts.(160)

Another method for measuring compliance involves the monitoring of prescription refill histories. Physicians interested in estimating an individual's compliance with their medication regimen may ascertain how frequently the prescription was refilled and the number of days between refills. However, the compliance of patients who possess free samples of the drug or who lose or share pills is impossible to determine: consequently, prescription monitoring is not generally considered an accurate method by which one can measure compliance.(151)

Compliance can also be assessed by counting the remaining number of pills and comparing that result with the number of pills that should be present given good compliance. As with self-reporting measures, there are a variety of methods by which the pill count may be altered, including misplacing the bottle, removing pills prior to an office visit, or taking a double dose of medication following a missed dosage.(151,161)

To assist compliance ascertainment, some individuals utilize the Medication Event Monitoring System (MEMS). MEMS are computerized pill bottles that have the ability to record the date and time that the bottle was opened, allowing a physician to track when and how frequently the

individual is taking their medications. This method is not without flaws, as an individual using AEDs may simply open the bottle, but not ingest the drug.(151)

Because of the problems associated with self-reporting and pill counting as means for measuring compliance, other methods are required. Non-invasive methods such as acquiring saliva, urine, or hair samples to determine the concentration of a particular drug in the individual's body.(162-164) Of these non-invasive methods, hair sampling appears to be the most useful, in that it can provide information about serum drug levels over an extended period. According to Williams, drugs enter the hair via passive diffusion, become sequestered and are then encapsulated in the hair shaft. The hair emerges above the scalp and becomes available for analysis, thus allowing determination of drug compliance at any particular time.(164) Hair sampling is not without drawbacks: it is not able to detect minor changes in compliance but, instead, only erratic or total noncompliance;(164,165) and the analysis it requires is complex and interpretation can be influenced by factors such as hair color, washing frequency, ethnic origin and chemical treatments.(165)

Both hair and saliva samples are said to agree well with trough plasma concentrations.(162,164) None of the articles reviewed commented on agreement rates between urine AED levels and blood serum concentrations.

Invasive methods for measuring AED treatment compliance

The most objective and widely accepted method for measuring compliance to a drug treatment regimen is to examine the level of the drug in the blood and determine whether that level falls within an expected therapeutic range. Ideally, within person, across time comparisons can be obtained to identify fluctuations in AED levels that are indicative of changes in compliance.(151,164) While more objective than self-reports, this method is not without its drawbacks, as detailed below.

1. With rapidly cleared medications, individuals can feign compliance by taking the medication in the days just before the blood draw, causing the test to demonstrate adequate drug concentrations.(151,161) However, if the medication being measured has a long half-life, the investigator will be provided with information on the preceding week or longer, giving a more accurate picture of the individual's medication taking behavior.(161)
2. Physicians must be mindful of such factors as time from last dosage, metabolism and age, as each of these variables affects serum concentration levels.(151) For example, if the person with epilepsy has a fever, they will eliminate the AED faster and show a lower serum concentration, which could mistakenly be interpreted as non-compliance.(16)
3. Physicians must also be aware of the other medications their patients are taking. For example, antacids have been found to decrease the absorption of phenytoin;(152) while the addition of another AED can affect concentrations of previously prescribed AEDs, or change the pharmacokinetic properties of one or both AED, as has been seen with a topiramate / phenytoin polytherapy.(16,166)

The comparison of blood levels across individuals may be a problematic approach, as natural variations in the concentration of the drug of interest occur from person to person. Similarly,

comparisons being made via drug serum level testing at different time points within the same person, may not serve to detect accurate dosing patterns.(167)

In addition, the concept of the "therapeutic range" is a broad generalization, with individuals requiring, and/or tolerating different medications at different dosage levels, depending on factors unique to that individual(16) While sub-therapeutic readings can indicate non-compliance, they may also suggest inadequate prescribing by the treating physician or simply be a reflective of a high sensitivity to the drug of interest.(168)

Because of the issues above, many researchers consider the variation in serum levels present across several (≥3) serum samples taken on different occasions; this measure of compliance being called the "coefficient of variation" (CV). At this time, however, CVs have only been established for carbamazepine, phenytoin, and valproic acid.(169) A CV of less than 20 percent for phenytoin and less than 25 percent for carbamazepine and valproic acid is considered an indicators of good compliance to treatment.(151,167)

Evidence Base Identification

We searched for studies of any design with a minimum of 10 subjects per arm that reported on both seizure frequency and compliance as measured by drug serum levels. The evidence-base development pathway for Key Question 5 is presented in Figure 21. Our searches identified a total of 847 articles. Of these, 126 articles appeared to be directly relevant to this key question and were retrieved. Many of the articles were drug trials that assessed the efficacy and tolerability of various AEDs or evaluating the effects of adding or withdrawing a medication. While many of these trials did measure drug serum concentrations and retention rates (how long a patient stayed on the drug, regardless of whether they went off the medication on their own or because the physician advised a change), they rarely reported on patient compliance.

Consequently, only five of the 126 retrieved articles met the inclusion criteria for this key question (Table 55). Table D-5 of Appendix D lists the 121 articles that were retrieved but then excluded and provides the reason for their exclusion. Detailed information pertinent to this section that has been extracted from the included studies is presented in *Study Summary Tables* that can be found in Appendix G.

Figure 21. Evidence Base Development Process

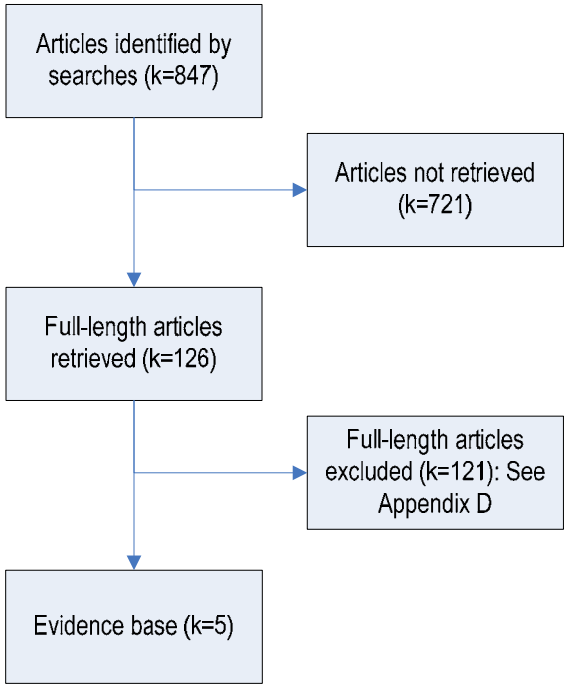


Table 55. Evidence Base for Medication Compliance and Seizure

Primary Reference	Year	Study Location	Country
Kemp et al.(170)	2007	Leeds	UK
Krauss et al.(94)	1999	Maryland	USA
Dilorio et al.(171)	1991	Georgia	USA
Peterson et al(172)	1984	Hobart	Australia
Wannamaker et al.(173)	1980	South Carolina	USA

Evidence Base

This subsection provides a brief description of the key attributes of the five included studies which reported information that provides insight into the relationship between AED treatment compliance (as measured by drug serum levels) and seizure frequency. Applicable information pertaining to study quality and the generalizability of each included study to drivers of CMVs is discussed later in the next sub-section of the evidence report. Detailed information pertinent to this section that has been extracted from the included studies is presented in Study Summary Tables that can be found in Appendix G.

The key attributes of each of the five included studies that address Key Question 5 are presented in Table 56. As per the inclusion criteria for this question, all five studies measured compliance with drug serum level and reported on seizure frequency. The five included studies utilized the

following designs: randomized controlled trial (k=2); case-control study (k=2); and cohort study (k=1).

All five included studies were small, with sample sizes ranging from 30 to 64. Study populations for all but Krauss et al. were made up of individuals with epilepsy who attended outpatient hospitals or specialist clinics. The cases included in the study of Krauss et al. differed from the other four included studies in that they consisted of individuals with epilepsy who had experienced a seizure-related crash. The control group in this study consisted of a matched group of individuals with epilepsy who did not crash who were identified through a review of medical charts from tertiary or primary care centers.

The main purpose of the Krauss et al. study was to determine the risk factors (including compliance) associated with a seizure-related crash. Both the Kemp et al. and DiIorio et al. studies main goal was to assess how factors such as individual beliefs about health affected compliance with AEDs. The Peterson et al. trial attempted to evaluate if compliance educational materials and compliance improvement strategies actually increased compliance rates, while the Wannamaker et al. trial investigated the effect of more frequent clinic visits on medication compliance and the role of the non-physician in providing healthcare to individuals with epilepsy.

Krauss et al. measured compliance using blood serum levels from patient records for 12 months prior to either the crash (for those individuals experiencing a crash), or 12 months prior to study inclusion for the non-crash subjects. He also reported on seizure frequency for the crash and non-crash groups, based on self report and medical record data. While the purpose of the study was not to investigate the relationship between seizure frequency and adherence, both of these variables were considered in relation to the risk of having a seizure-related crash. The remaining four studies directly examined the relationship between seizure rates and compliance. The retrospective cohort studies divided individuals with epilepsy into compliant and non-compliant groups and compared the seizure rates in each group. DiIorio et al. used an average serum level to categorize her subjects' compliance; Kemp et al. graded individuals with epilepsy on a 5 point scale from poor to excellent adherence and, then, based on the mean adherence score in the sample, divided subjects into high (above the mean) or low (below the mean) adherers.

Peterson et al. categorized his subjects as within, above or below the therapeutic range for their given AED using chart data covering the period from six months prior to study initiation to the six month follow-up visit. Compliance rates for the compliance education group versus the no compliance intervention subjects were compared, and the median number of seizures pre- and post study were examined. Wannamaker et al. classified individuals as good, fair, poor or none in terms of average baseline and follow-up AED levels, using generally accepted therapeutic ranges as a guide for these categories. Baseline AED level was established from chart notes covering the period of 6 to 12 months preceding the study. For the baseline AED level, he took the mean AED level from subjects' chart notes for the six to Follow-up constituted the averaged AED levels for the entire six month study period, including the first and second half of the study periods. In addition, Wannamaker et al. calculated an average seizure frequency for similar time frames pre and post-study initiation.

Table 56. Study Design Characteristics of Studies that Address Key Question 5 – Medication Compliance and Seizure Control

Reference	Year	Size (N=)	Study design	Prospective or Retrospective	Aim of study	Study population	Method used to measure compliance	Method used to measure seizure
Kemp et al.(170)	2007	37	Cohort	Retrospective	Determine the influence of beliefs about epilepsy, beliefs about medication and a range of variables on drug adherence.	Individuals with diagnosis of epilepsy recruited from a local epilepsy outpatient clinic.	5 point rating scale used to categorize level of compliance: 5 excellent adherence, 4 good, 2-3 incomplete/partial adherence, 1 poor adherence. Ratings were cross checked by two of the authors; also categorized as low (<3.9) or high (>3.9) on adherence.	Self report on time since last seizure.
Krauss et al.(94)	1999	100	Case control	Retrospective	To determine risk factors associated with motor vehicle crashes.	50 individuals with epilepsy with driving crashes during seizure compared with 50 individuals with epilepsy who drove but did not have crashes. Crash subjects identified from chart review of three Maryland hospital-based outpatient epilepsy clinics. Controls selected by alphabetical review from two tertiary and one primary referral populations.	AED levels taken from patient charts for 12 months prior to crash or, for controls, the 12 month period beginning in mid-1996. Data on self-report compliance was also gathered.	Self-report and record review. For crash related seizure and other seizures.
Dilorio et al.(171)	1991	64	Cohort	Retrospective	To explore cognitive-perceptual factors discussed in the compliance literature (uncertainty in illness, health conception, and social support) but not yet examined in patients with epilepsy.	Subjects recruited from outpatient epilepsy clinic of a public hospital serving low socioeconomic status patients.	Individuals categorized as compliant or non-compliant based on average of serum blood draws taken day of study entry and all readings in three months prior to study entry. Values in therapeutic range were considered compliant and values 30% or more below therapeutic range indicated non-compliance. Nurses and Physicians also subjectively classified individuals as compliant or noncompliant. Only subjects with 100% congruence between objective and subjective measures were included in the study.	Self report of number of seizures in last year and number of weeks since last seizure.

Reference	Year	Size (N=)	Study design	Prospective or Retrospective	Aim of study	Study population	Method used to measure compliance	Method used to measure seizure
Peterson et al.(172)	1984	53	RCT	Prospective	To determine if a combination of easy to implement and inexpensive strategies can improve medication compliance.	Consecutive adult and teenage outpatients with epilepsy responsible for administering their own medication and who possessed a hospital pharmacy book. 27 individuals randomly allocated to receive compliance counseling, pill holder, seizure diary, prescription, and appointment reminders. Remaining 26 individuals allocated to a no intervention control group	Serum levels considered in therapeutic range were phenytoin 40-80; carbamazepine 20-40; sodium valproate 300-600. Plasma levels were examined in three ways: categorized as below, within or above therapeutic levels; plasma levels by dose and absolute plasma levels.	Median number of seizures during 6 months preceding study intervention (baseline) and at follow-up was calculated.
Wannamaker et al.(173)	1980	30	RCT	Prospective	To determine the effect of more frequent clinic visits on compliance and the role of the non-physician in managing individuals with epilepsy.	Subjects were recruited from an outpatient seizure unit within a hospital. All but two were adults. All were individuals with epilepsy on a stable drug regimen for six months or more. Thirty individuals were randomized to receive either treatment by a neurologist (N=14) or by a clinical pharmacist (N=16).	Baseline serum levels in the six to 12 months preceding the study were averaged. For follow-up, AED plasma levels were averaged for the first three months, the last three months and all six months of the study period combined. Each average was assigned a ranking of good, fair, poor or none based on "generally accepted" therapeutic ranges. Ranking status for AEDs were: Carbamazepine >4.0ug/ ml good,3.9-2.5 ug/ml fair, 2.4-1.5 ug/ml poor, <1.5 ug/ml none; Phenobarbital >15.0 ug/ ml good, 14.9-10.0 ug/ml fair, 9.9-5.0 ug/ml poor, <5.0 ug/ml none; Phenytoin >10.0 good, 9.9-5.0 ug/ml fair, 4.9-2.0 ug/ml poor, <2.0 ug/ml none. An improvement in compliance was defined as a shift upward by one rank. It had to occur in the last three months of the study period or had to be sustained throughout the entire six months.	Seizure was measured by self report. Seizure frequency was averaged for the six months preceding the study and for the six months following study initiation. Seizure status was considered improved if there was a 50% or greater reduction in frequency.

Quality of the Evidence

The results of our analysis of the overall quality of the evidence base for Key Question 5 are presented in Table 57. Our assessment found that the quality of the included studies ranged from low to moderate. Although two of the five studies were randomized controlled trials, there were methodological problems with both studies that reduced their quality scores. In the Peterson et al. study, the two groups used were not comparable at baseline on some important patient characteristics such as baseline AED levels and median number of seizures, suggesting randomization failure. The Wannamaker et al. trial did not report key pieces of information such as important baseline characteristics of the two study groups or the group to which individuals who required dosage changes during the study were assigned.

Differences in the compliance education intervention group and the no intervention group make interpretation of the Peterson et al. study difficult. For example, the two groups in this study started out unequal, with the no intervention group having a lower, though not statistically significantly lower, median seizure rate compared with the compliance education group. At follow up, the compliance education group had a median seizure rate that was slightly less than that of the no intervention subjects. However, it is unclear if the compliance education group experienced a drop in seizure rates over the course of the study because the intervention provided was effective or if they were merely recruited into the study at a point in time when they happened to be at a high phase and would have experienced a decline without any intervention at all.

Case-control and cohort studies are susceptible to bias, meaning that even a perfectly designed and executed case-control study cannot be graded as high quality. While those conducting case control trials may be able to control for subject characteristics likely to affect the outcome of interest, the relationship between the research outcome being studied and all subject characteristics cannot be known. Only randomization is able to control for these unknown confounders. Similarly, in cohort studies there is no way of knowing how the groups being compared differ and how this may affect the study results.

Table 57. Quality of Studies of Medication Compliance and Seizure Control

Reference	Year	Quality Scale Used	Quality Score	Quality
RCT of compliance education material versus no educational material				
Peterson et al.(172)	1984	ECRI Assessment Tool for Controlled Interventional Studies that have Independent Groups	6.7	Moderate
Wannamaker et al.(173)	1980	ECRI Assessment Tool for Controlled Interventional Studies that have Independent Groups	5.9	Moderate
Cohort Studies				
Kemp et al.(170)	2007	Revised Newcastle-Ottawa Quality Assessment Scale Cohort Studies	6.15	Low
Dilorio et al.(171)	1991	Revised Newcastle-Ottawa Quality Assessment Scale Cohort Studies	5.58	Low
Case Control Study				
Krauss et al.(94)	1999	Revised Newcastle-Ottawa Quality Assessment Scale Case Control Studies	7.88	Low

Generalizability of Evidence to Target Population

Table 58 presents information on patient characteristics for each of the five included studies. None of the studies that comprise the evidence base for Key Question 5 specifically included information about the occupations of the participants. Given this, and the heterogeneity of the populations represented in the included studies, one is precluded from making a definitive statement about the generalizability of the evidence to the target population of interest to FMCSA (CMV drivers).

Krauss et al.'s study of seizure-related crashes included a sample of epileptic drivers that was predominantly male (82 percent for crashes and sex matched controls)In the remaining four studies, between 37.5 percent and 58 percent of subjects were male. Krauss et al. also matched on age (within three years). The average age of Krauss et al's crash cases was 38.5 years (range: 21–70 years) and for non crash cases 39.8 years (range 18–73 years). DiIorio et al.'s compliant subjects were 35.56±11.26 years on average while her noncompliant subjects were 36.56±13.68 years of age (Range: 17–79, Mean age: 40.77). The median ages of Peterson et al.'s compliance education and no compliance education groups were 28 (range: 18–64) and 35 (range: 19–74), respectively. Wannamaker et al's neurologist- and pharmacist-treated groups were 26 (range: 14–50) and 29 (range: 15–52) years of age on average, respectively. Each group was made up of adults with epilepsy, plus one minor, fourteen years of age.

Only the Kemp et al. study reported on age of onset of epilepsy. Kemp et al.'s subjects developed epilepsy at 25.86 years (range 0–77), on average.

Neither Krauss et al., or DiIorio et al. reported which AEDs were used by the individuals in the study. Kemp et al.'s reported that individuals in the study were using lamotrigine or a polytherapy of lamotrigine and low dose phenobarbitol. Percentages for monotherapy versus polytherapy were not reported. Peterson et al.'s groups contained monotherapy and polytherapy, although percentages for each group were not provided. Overall, the compliance group utilized phenytoin, carbamazepine, valproate, and 'other AED'. The non-compliance group Of the individuals in Peterson et al.'s compliance education group utilized phenytoin, carbamazepine, valproate, and 'other AEDs'. Wannamaker et al. presented combined AED data for both groups, with three patients(10 percent) receiving phenytoin, one (3.3 percent) receiving phenobarbitol, and one (3.3 percent) receiving primidone. The remaining subjects utilized polytherapy, including carbamazepine, acetazolamide, clonazepam, clorazepate, dipotassium, dextroamphetamine, ethosuximide and methylphenidate.

Like Peterson et al., neither the Krauss et al. nor Kemp et al. studies reported information on polytherapy use by their subjects. DiIorio et al. reported the mean number of AEDs being taken by the compliant patients in her sample was 1.49±.56 compared with 1.44±.51 among noncompliers. In the Wannamaker et al. study 83.3 percent (25 out of 30 subjects) or utilized polytherapy.

Krauss et al.'s subjects suffered primarily from CPS (52 percent of both crashes and non-crashes). The next most common form of seizure among Krauss et al's subjects was GTCSs at 36 percent of both groups: secondary generalized seizures occurring in 26 percent of the crash group and 24 percent of the non crash group; and simple partial seizures occurring in 12 percent and 20 percent of his subjects, respectively. It should be kept in mind for all of the studies that a single individual could report experiencing multiple types of seizures. Kemp et al. did not report any

information on the type of epilepsy suffered by his research subjects. In DiIorio et al.'s study, 18 percent of compliant subjects reported experiencing generalized seizures, 44 percent partial with generalized, 2 percent simple partial and 36 percent complex partial. Among DiIorio et al.'s noncompliers, 32 percent reported generalized, 24 percent partial with generalized, 44 percent complex partial and no patients reported simple partial seizures. Unlike Krauss et al.' subjects, participants in the DiIorio study were not able to report multiple answers to this question. Peterson et al.'s subjects, too, were categorized by a single seizure type only. Among study participants receiving compliance education, 52 percent suffered from GTCSs, 19 percent partial with secondary generalization, 15 percent complex partial, and 15 percent experienced other types of seizures. In the no education group, 65 percent had GTCSs, 12 percent partial with secondary generalization, 15 percent complex partial and 8 percent had another type. Wannamaker et al. did not report on type of seizure.

Krauss et al., Peterson et al., and Wannamaker et al. did not provide information on their subjects' duration of epilepsy. Kemp et al. reports that his sample had had epilepsy for an average of 14.51 years (range 1 – 63 years duration). DiIorio et al. reports that her compliant subjects had epilepsy for 18.69±11.97 years versus 13.40±10.83 years for non compliant patients.

None of the five studies reported on comorbidities or the percent of their sample that was made up of CMV drivers. Therefore, the generalizability of these five studies' results to CMV drivers is unknown.

Table 58. Patient Characteristics

Study	Group	n=	% male	Age	Age at onset of epilepsy	AED	% patients on polytherapy	Type of epilepsy	Duration of epilepsy (yrs)	Co-morbidities	% CMV drivers	Generalizability to CMV drivers
Cohort Studies												
Kemp et al.(170)	Compliers and non compliers	37	51.4	Mn = 40.77 Rng =17-79	Mn = 25.86 Rng = 0-77	Lamotrigine or Lamotrigine and Phenobarbital 100%	NR	NR	Mn = 14.51 Rng = 1-63	NR	NR	Unknown
Dilorio et al.(171)	compliant	39	54	Mn = 35.56 SD = 11.26	NR	NR	Mn # of drugs= 1.49 (SD) = .56	Generalized 18% Partial with generalized 44% Simple partial 2% Complex partial 36%	Mn = 18.69 (SD) = 11.97	NR	NR	Unknown
	non-compliant	25	48	Mn = 36.56 SD =13.68	NR	NR	Mn # of drugs = 1.44 (SD) = .51	Generalized 32% Partial with generalized 24% Simple partial 0% Complex partial 44%	Mn = 13.40 (SD) = 10.83	NR	NR	Unknown
Case Control Study												
Krauss et al.(94)	crashed	50	82	Mn = 38.5 Rng = 21-70	NR	NR	NR	GTCSs 36% Secondary generalized 26% Simple partial 12% Complex partial 52%	NR	NR	NR	Unknown
	did not crash	50	82	Mn = 39.8 Rng = 18-73	NR	NR	NR	GTCSs 36% Secondary generalized 24% Simple partial 20% Complex partial 52%	NR	NR	NR	Unknown
RCT of compliance educational material versus no educational material												
Peterson et al.(172)	with compliance education	27	56	Mdn = 28 Rng = 18-64	NR	Phenytoin 74% carbamazepine 52% Sodium valproate 30% Other 11%	NR	GTCSs 52% Partial with secondary generalization 19% Complex partial 15% Other 15%	NR	NR	NR	Unknown
	no compliance education	26	58	Mdn = 35 Rng = 19-74	NR	Phenytoin 89% Carbamazepin	NR	GTCSs 65% Partial with secondary generalization 12%	NR	NR	NR	Unknown

Study	Group	n=	% male	Age	Age at onset of epilepsy	AED	% patients on polytherapy	Type of epilepsy	Duration of epilepsy (yrs)	Co-morbidities	% CMV drivers	Generalizability to CMV drivers
						e 19% Sodium valproate 19% Other 19%		Complex partial 15% Other 8%				
Wannamaker et al.(173)	14	50	Mn = 26 Rng = 14-50	NR	Three phenytoin, one phenobarbitol, one primidone, 25 polytherapy	83.3	NR	NR	NR	NR	NR	Unknown
	16	37.5	Mn = 29 Rng = 14-52	NR			NR	NR	NR	NR	NR	Unknown

Findings

The findings of the five studies that addressed Key Question 5 are presented in Table 59. Of these five studies, two addressed the question directly. A further three studies addressed the question tangentially. One of these latter studies is of particular importance because it addresses the larger issue of whether non-compliance with an AED regimen has an impact on crash risk.

Krauss et al. found that the one-third of patients in both the crash and no crash group were noncompliant with AEDs. This finding suggests that noncompliance has little, if any impact on crash risk. The investigators found that the single factor most strongly associated with crash was a short seizure free interval. Krauss reported that risk of a crash was significantly reduced among individuals who had been seizure free for at least 12 months. Surprisingly, seizure frequency was found to be a less reliable risk factor for experiencing a crash. This may be explained by the statistical methods used in the Krauss et al study. The investigators conducted a multivariate analysis to see which factors were most closely related to crash. In multivariate analysis, the influence of each variable on the outcome of interest is examined while all of the other variables in the equation are held constant, so that the effect of each individual factor can be estimated. While the crash cases had significantly more seizures than the non-crash cases at baseline, when only patients with similar frequency of seizures were compared, an extended seizure free interval was more important.

The second study to address Key Question 5 (Peterson et al.) was conducted to determine the effectiveness of an AED compliance education program. In a randomized controlled trial, Peterson et al. compared the percentage of patients who received compliance education with that among individuals who did not receive the program. Outcomes assessed at 6 months follow up included AED plasma levels and median seizure frequency. The study investigators found at follow up there was a significant difference between the two study groups in compliance with a higher proportion of individuals who received compliance education having AED serum levels that fell within the therapeutic range. This group also demonstrated a concurrent, significant decline in seizure frequency. In contrast, individuals who did not receive compliance education did not become more compliant nor did they experience reductions in seizures over time. This finding provides some indirect evidence to suggest that compliance and seizure frequency are closely related with increased compliance leading to reductions in seizure frequency.

Like Peterson et al., the Wannamaker et al. trial was interested in the effectiveness of an intervention for increasing medication compliance: specifically, they studied the impact of more frequent clinic visits and treatment by non-physicians on compliance with AEDs.(173) They compared compliance with medication before and after the increase in clinic visit frequency and compliance rates for those treated by neurologists and clinical pharmacists. In terms of our Key Question, they found that following an increase in clinic visits, 11 study participants showed improvement in AED compliance, two showed a decline, and eight experienced a reduction in seizures. However, only one subject showed improvement in both compliance and seizure frequency. Unlike Peterson et al, Wannamaker et al.'s results suggest that increased compliance may not lead to greater seizure control.

The remaining two studies that addressed Key Question 5 did so directly.(170,171) Kemp et al. found a significant relationship between serum AED level and the number of days since last

seizure ($r = 0.39$, $p < 0.05$).(170) In addition, when these investigators stratified individuals into compliers and non-compliers they found that the time since last seizure was significantly shorter among poor compliers than among patients with good compliance. DiIorio et al. however, did not identify a relationship between compliers and noncompliers either in terms of number of seizures experienced in the last year or number of weeks since last seizure.(171)

Table 59. Findings

Study	n	Groups	Length of Follow-up	#s compared	Statistic used	Relationship of compliance to seizure
Cohort Studies						
Kemp et al.(170)	22	Compliant	Data gathered in one day, asked about mean time since last seizure (days)	NR	Mann Whitney U = 62.5 p < 0.01, also presented correlation coefficient =0.39 p <0.05 for adherence and time since last seizure in days.	Patients with low adherence scores had significantly less time since last seizure relative to high compliers.
	15	Non-compliant				
Dilorio et al.(171)	39	Compliant	Data on seizure gathered in one day, used average serum, no info on from how long ago, data collection lasted six months.	<u>*# of seizures in the last year*</u> Mn = 23.44 (SD) = 36.64 <u>*# weeks since last seizure*</u> Mn = 14.59 (SD) = 24.28	t-test, t=NR; P=NS	No relationship between compliance and seizure.
	25	Non-compliant		<u>*# of seizures in the last year*</u> Mn = 13.36 (SD) = 19.99 <u>*# weeks since last seizure*</u> Mn = 10.80 (SD) = 23.07		
Case Control Study						
Krauss et al.(94)	50	Crashes	12 months preceding the crash	<u>*Seizure frequency, average per month*</u> Mn 2.6 Rng = 0-60 1/3 of patients classified as non-compliant	Wilcoxon signed rank test for seizure frequency, z = -2.62, two-tailed p =0.009	Patients who crashed had significantly higher seizure frequencies than non crash cases, but in terms of risk factors for a crash, seizure frequency was not as important as seizure free interval. Because approximately one-third of both groups had episodes of AED noncompliance during the study year, there was no increase in the odds of crashing associated with AED noncompliance.
	50	Non Crashes	12 months beginning in mid-1996	<u>*Seizure frequency, average per month*</u> Mn 0.6 Rng = 0-6 1/3 of patients classified as non-compliant		
Randomized Controlled Trial						

Peterson et al(172)	27	Compliance Education	12 month period, 6 months preceding study entry through 6 month follow-up	# seizures in 6 months prior to intervention
				Mdn = 6
				Rng = 0-55
					For AED levels, Stuart Maxwell chi-square =13.78, p<.005 for pre- versus post-intervention in education group
					For AED levels, Stuart Maxwell chi-square =1.0, p>.10 for pre- versus post-intervention in the no
						The compliance education group was more compliant following education while the no education group did not become more compliant over time. The education group also experienced a reduction in seizure frequency

Study	n	Groups	Length of Follow-up	#s compared	Statistic used	Relationship of compliance to seizure

				# seizures at follow up
				Mdn = 2.5
				Pre- intervention
				54% of AED levels below therapeutic range
				Post-intervention
				12% of AED levels below therapeutic range
					education group
					For seizure, Wilcoxon T p<.01 for pre versus post intervention for compliance education group and Wilcoxon T for no education group was p>0.1.
						after receiving the educational intervention, while the no education group did not experience a drop in seizures over time.

	26	No Compliance Education		*# seizures in 6 months prior to intervention* Mdn = 4 Rng = 0-51 *# seizures at follow up* Mdn = 3.5 *Pre- intervention* 45% of AED levels below therapeutic range *Post-intervention* 52% of AED levels below therapeutic range		
Wannamaker et al.(173)	14	Neurologist treated	Six to 12 months preceding study and six month study follow-up	Did not compare neurologist versus pharmacist treated groups except to state that there was no difference in the degree of improvement of AEDs between groups. Overall, 10 pts improved on compliance alone, eight on seizure alone, and one on both.	No statistical tests performed, but did create confidence intervals around study findings	"No correlation between increased AEDL and reduction in seizure frequency."
	16	Pharmacist treated				

Section Summary

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, he 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 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, is 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? Surrogate markers of driver safety consist of the following:

a. Driving performance (simulated or closed course)

b. Cognitive and psychomotor function

Background

Our analysis of Key Question 1 found that individuals with recurrent unprovoked seizures are at an increased risk for motor vehicle crash when compared to comparable individuals who do not have the disorder. In this section we attempt to determine the extent to which, chronic[12] AED use might contribute toward this increased crash risk.

[12] Defined for this report as > 2 weeks

It is conjectured that antiepileptic medications may have broad effects on cognitive (e.g. memory) and psychomotor (e.g. reaction time, coordination, and tracking) abilities, with different AEDs having different risks of cognitive and psychomotor impairment, different therapeutic doses, titration rates, and/or blood serum levels having different risks of cognitive and psychomotor impairment for the same AED, and the use of multiple AED therapies (polytherapy) to affect seizure control being widely associated with an increase in cognitive impairment.(166,174-177)

Measuring Driver-Related Cognitive and Psychomotor Function

Studies of cognitive (information processing, long and short-term memory, reasoning) and psychomotor (simple reaction time, choice reaction time, coordination and tracking) skills(178) hypothesized to be affected by AED treatment employ a wide variety of testing tools: in the studies included in this report approximately 62 separate tests were used to measure cognitive and psychomotor skills. A partial listing of these tests includes:

- Benton Visual Retention Test
- Finger Tapping Test
- Choice Reaction Time
- Simple Reaction Time
- Lafayette Grooved Pegboard
- Paired Words Test
- Stroop Color Word Test
- Rey Auditory Verbal Learning Test
- Performance on Line Test
- Symbol Digit Modalities Test
- Digit Symbol Substitution Test
- Critical Flicker Function

Recognizing that "no single test can be used to predict the effect of a drug on cognition or on the diverse and complex skills involved in everyday tasks, such as driving a car,"(179) an effort was made to identify the cognitive and psychomotor tests which might be most relevant to assessments of driving skill. A survey of the literature in drug-related performance impairment was conducted, and tests were chosen on the basis of their ability to fulfill the driving-related cognitive domain criteria enumerated below.

According to Kay (*Measuring Impairment: Validated Test Methods for Assessing Sedating Medication*s, 2001),(180) sedation is "depression of brain functioning by a medication, manifested by" the following:

- Sleepiness, drowsiness or fatigue
- Slowed brain activity

- Reduced wakefulness
- Impaired performance

Using this definition of sedation, one can logically conclude that an investigation of the cognitive (e.g. slowed brain activity) and psychomotor (e.g. impaired performance) effects of antiepileptic medications on the central nervous system could be considered an attempt to document the sedative effects of AEDs. Specific performance measures which evaluate the sedative effects of medications include simulation, cognitive testing, and psychomotor testing. Critical cognitive domains for demonstrating sedation include:

- Vigilance: the capacity to sustain attention under conditions of minimal arousal. These tests "appear to be the most sensitive measures for detecting the sedation effects that may contribute to accidents"(180)
- Divided attention: ability to perform simultaneous mental activities (also referred to as 'dual tasking')
- Working memory: the ability to hold information temporarily in the brain for purposes of using the information in a calculation, or other mental activity

The list of tests used to identify cognitive and psychomotor functions underlying driving performance according to the framework identified by Kay(180) were obtained through a survey of the literature(180-188) and examination of methodology employed by a research center which specializes in assessing the influence of psychopharmacological agents on driving performance (University of Maastricht Psychology Lab).(189) Using the three domains as the framework, the total list of cognitive and psychomotor tests employed by all included studies in this report (n = 52; see Appendix M for the total list) were examined and grouped under their respective domains. The lists of cognitive and psychomotor tests from the literature/research center survey and the included studies table were then compared. Those tests which did not agree between the two lists were eliminated, to create a final list of 12 cognitive and psychomotor tests (listed above).

A meta-analysis exploring the relationship between neuropsychological functioning and driving ability in dementia by Reger et al.(190) categorized a series of neuropsychological tests into six cognitive domains: mental status-general cognition; attention/concentration; visuospatial skills; memory; executive function; and language. The meta-analysis concluded that driving ability tended to decline as cognitive functioning declined.

The only tests discussed in Reger's meta-analysis which demonstrated significant relationships with on-road tests (tests actually performed in a vehicle) were in the visuospatial skills and attention/concentration cognitive domains. Problems with on-road tests include high cost, observer subjectivity, and inability to control real-world variables such as road conditions and the behavior of other drivers. For non-road tests (which have the advantage of allowing more control over conditions and variables), mental status/general cognition, visuospatial skills, memory, and executive functions all demonstrated significant relationships.

The meta-analysis reported several limitations (all related to the primary studies utilized) including variability in participant characteristics, data reporting, driving measures, and the widely held assumption that driving tests are valid and reliable. Of special importance to this

section is the acknowledgment of the wide variety of cognitive tests used in the studies included in the meta-analysis: as many of the tests examine multiple cognitive domains and may test different aspects of each domain, assembling them into broader categories may reduce only a small part of the variability inherent in any effort to group somewhat different articles into a single defined entity.

Keeping this acknowledgement in mind, the total list of 12 cognitive and psychomotor tests used in the studies included in this report was compared to those tests included in Reger et al.'s six cognitive domains. Ultimately it was found that the cognitive and psychomotor tests in centered around the attention/concentration domain (k=3), the executive function domain (k=1) and the memory domain (k=1). Comparing the list to Kay's three domain criteria found that the cognitive and psychomotor tests centered around the psychomotor domain (k=3) and vigilance domain (k=2), with the remaining domains each having one example present: visual processing, working memory, memory and cognition, and verbal memory. Areas of overlap between Kay's domains and Reger's domains included attention/concentration (k=2), executive function (k=1), and memory (k=1).

Findings of Previous Reviews

A number of recent reviews have discussed the potential effects of AEDs on the cognitive and psychomotor function of individuals with recurrent seizure disorder.(174,175,191-198) Evidence cited in these reviews provides evidence that the acute and chronic use of some AEDs does have a deleterious impact on both cognitive and psychomotor function in some individuals. While these reviews are valuable in helping to determine the potential effects of chronic AED use, they are of limited value to FMCSA. For example, the vast majority of studies included in the reviews are short-term studies that include a high proportion of children, a population that is clearly not relevant to a report on the potential effects of AEDs on CMV drivers. Another factor is shared by many of the articles included in the reviews cited above which limits their value in a review aimed at a CMV driver population. This factor is that most studies were not designed to study the effects of AEDs on aspects of cognitive and psychomotor function that are thought to be pertinent to the task of driving.

Identification of Evidence Base

In attempting to address Key Question 6 we searched for trials that compared driving performance (simulated or experimental) or cognitive and/or psychomotor function among individuals with epilepsy treated with at least one AED and individuals who are not treated with such drugs but who are otherwise comparable.

The identification of the evidence used in this section of the Evidence Report is presented in Figure 22. Our searches[13] identified a total of 1849 articles that appeared relevant. Following application of the retrieval criteria for this question, 496 full-length articles were retrieved and read in full. Two of the 496 retrieved articles were found to meet our criteria for inclusion. Table 60 lists the two articles that met the inclusion criteria for Key Question 6. Table D-6 of Appendix D lists the 494 articles that were retrieved but then excluded and provides the reason for their

[13] See Appendix A for search strategies

exclusion. A total of 340 articles included in the excluded studies table were used to provide reference and background material for this section of the report.

Figure 22. Development of Evidence Base for Key Question 6

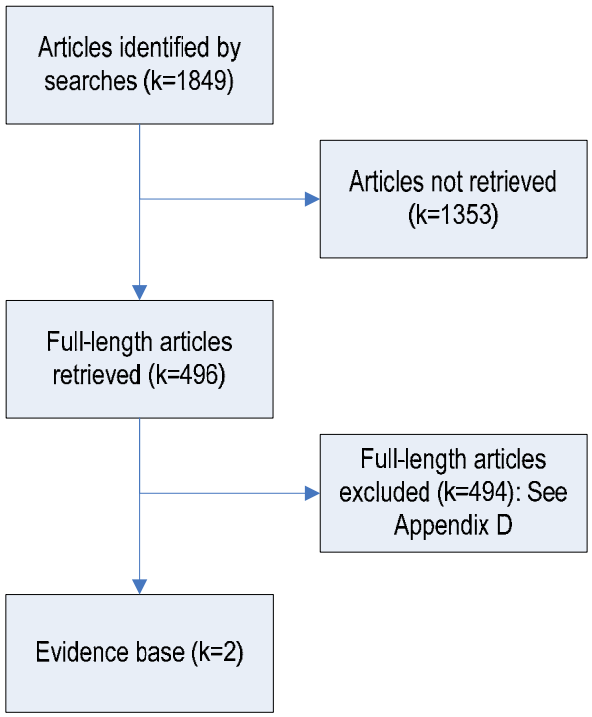


Table 60. Evidence Base for Key Question 6

Reference	Year	Study Location	Country
Engelberts et al.(199)	2002	Heemstede	Netherlands
Hessen et al.(200)	2006	Oslo	Norway

Evidence Base

This subsection provides a brief description of the key attributes of the two studies that met the inclusion criteria for Key Question 6. Here we discuss relevant information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of CMVs. Detailed information pertinent to this section that has been extracted from included studies is presented in the *Study Summary Tables* that comprise Appendix G.

Characteristics of Included Studies

The primary characteristics of the two included studies that address Key Question 6 are presented in Table 61. Neither included study examined the effects of chronic AED use on cognitive and/or psychomotor function. Consequently, one cannot draw evidence-based conclusions pertaining to the effects of these drugs, when used to treat individuals with epilepsy, on driving performance.

Table 61. Key Study Design Characteristics of Studies that Address Key Question 6

Reference	Year	Research question	Drug examined	Study Design	Follow-up Time	Comparison	Outcomes assessed
Engelberts et al.(199)	2002	To investigate whether well-controlled epilepsy patients with late age at onset and long duration of epilepsy who have been seizure-free for more than 2 years have impaired objective neuropsychological functioning.	Carbamazepine	Non-randomized controlled trial Blinding – Not Reported (NR) Prospective	No follow-up. Comparison involved a single day of testing	16 individuals with well-controlled epilepsy compared to 16 age, gender, and education-matched healthy volunteers (defined as individuals without epilepsy) on neuropsychological functioning.	Rey Auditory Verbal Learning Test Stroop Test
Hessen et al.(200)	2006	To assess the effect of discontinuation of AEDs in patients receiving monotherapy on measures of attention, reaction time, and speed of information processing	Carbamazepine Sodium valproate	Randomized Controlled trial Blinding: Double-blind Prospective	52 weeks or until seizure relapse	79 patients without AED withdrawal underwent cognitive testing 71 patients randomized to planned AED withdrawal (over a period of 12 weeks)underwent cognitive testing	Simple Reaction Time Choice Reaction Time Sequential Reaction Time Language Discrimination Degraded words distract Response reversal Form discrimination

Hessen et al.(200) conducted a randomized, double-blind, placebo-controlled prospective study to assess the effect of discontinuation of AED monotherapy on measures of attention, reaction time, and speed of information processing. Specifically, 150 individuals who had been seizure free for a minimum of two years on AED monotherapy discontinued the therapy, and then went through a randomization process to either: 1) resume AED therapy or, 2) begin placebo 'therapy.' Participants were included in the study if they had a diagnosis of epilepsy (two unprovoked seizures or more), were free of seizures for a minimum of two years, were using AED monotherapy, were between the ages of 18 and 67, and had five years of seizure freedom if prior discontinuation was unsuccessful. Participants were excluded from the study if they had juvenile myoclonic epilepsy, polypharmacy, paroxysmal epileptiform activity with primarily generalized epilepsy, two prior AED discontinuation attempts, were pregnant or seeking pregnancy, mental retardation, progressive neurologic disease, other serious diseases that may influence the health status of the patient in the study period, or co-medication (expect postmenopausal hormone substitution), ASA, and thyroxin. The outcome measures used in this study were scores in the following cognitive and psychomotor tests: simple reaction time (SRT), choice reaction time (CRT), sequential reaction time, rapid language discrimination, visual selective attention, response reversal and rapid visual screening, and form discrimination.

Engelberts et al.(199) conducted a non-randomized, controlled, prospective study to determine whether individuals with well-controlled epilepsy with late age at onset and long duration of epilepsy would have impaired objective neuropsychological functioning. Specifically, 16 individuals who had been seizure free for more than two years on AED monotherapy were compared with 16 healthy, age-, gender-, and education-matched controls on measures of cognitive and psychomotor functioning. Participants were included in the study if they had partial epilepsy, utilized carbamazepine (CBZ) monotherapy, and were between 18 and 65 years of age. Participants were excluded from the study if they presently used psychoactive drugs or AEDs other than CBZ, had additional neurological or psychiatric disease, had severe perceptual deficits, or had a history of head injury, status epilepticus, neurosurgery, or neuropsychological evaluation within the last year. The outcomes measures used in this study were scores in the following cognitive and psychomotor tests: Stroop Color-Word test (selective attention), Auditory Verbal Learning Test (AVLT, verbal memory), and the Categoric Word Fluency Task (Fluency, retrieval from semantic memory).

Quality of Evidence Base

The results of our assessment of the quality of the two studies that address Key Question 6 are presented in Table 62. This assessment found that the quality of one study was high (Hessen et al.) and the other study was of low quality (Engelberts et al.). The primary reason for moderate quality was: failure to report funding sources (one study). The primary reasons for low quality were lack of randomization and blinding (one study). Both of the studies were prospective.

Table 62. Quality of the studies that Assess Key Question 6

Reference	Year	Quality Scale Used (see Appendix F)	Quality Score	Quality
Engelberts et al.(199)	2002	ECRI Quality Scale I-Comparative Trials	5.0	Low

Reference	Year	Quality Scale Used (see Appendix F)	Quality Score	Quality
Hessen et al.(200)	2006	ECRI Quality Scale I-Comparative Trials	8.2	High

Generalizability of Evidence to Target Population

The purpose of this subsection is to provide details of the extent to which the individuals enrolled in the studies that address Key Question 6 are similar to CMV drivers in the United States. Important characteristics of the individuals included in the studies that address Key Question 6 are presented in Table 63.

The generalizability of the individuals enrolled in the two included studies to CMV drivers is unclear. Neither of the studies included information about the occupation or the driving experience of the participants, making it difficult to generalize on the basis of employment or driving exposure. Other factors that may limit the generalizability of the findings of the two studies to the target population includes the proportion of women in the included studies, which is higher than the prevalence of female CMV drivers. Similarly, while the age of the participants in the studies was over 18, the comparison may have limited generalizability as CMV drivers in the United States tend to be older (over 40 years of age) and often have a number of comorbidities such as cardiovascular disease and diabetes mellitus which were excluded in both studies.

Table 63. Individuals Enrolled in Studies that Address Key Question 6b

Reference	Year	Treatment Group	Age distribution	Disease state	Seizure Frequency per 28 days at Baseline	Length of education	%Male	%White	Driving experience	Generalizability to CMV drivers
Engelberts et al.(199)	2002	Carbamazepine (n=16)	Mean: 45.9 (SD: 10.3) years	Simple partial seizures (n=2) Complex partial seizures (n=1) Simple partial seizures plus complex partial seizures (n=2) Simple partial seizures plus secondarily generalized seizures (n=2) Complex partial seizures plus secondarily generalized seizures (n=9)	NR	NR	67%	NR	NR	Unclear
		Control (no drug treatment group) (n=16)	NR	None	NA	NR	NR	NR	NR	Unclear
Hessen et al.(200)	2006	Treatment Group (n=71)	Mean: 39.2 (Range 19-65) years	Epilepsy (not defined)	NR	NR	60%	NR	NR	Unclear

Reference	Year	Treatment Group	Age distribution	Disease state	Seizure Frequency per 28 days at Baseline	Length of education	%Male	%White	Driving experience	Generalizability to CMV drivers
		Control Group (n=79)	Mean: 37.4 (Range 18-66) years	Epilepsy (not defined)	NR	NR	60%	NR	NR	Unclear

Findings

The findings of the two studies that met the inclusion criteria for Key Question 6 are presented in Table 64. As noted above, neither included study provided data pertaining to indirect measures of driving performance. Thus our findings are restricted to the effects of chronic effects of AEDs on cognitive and psychomotor functions pertinent to the task of driving.

Table 64. Cognitive and Psychomotor Function Following AED Administration

Reference	Year	Comparison	Test and Findings	Conclusion
Engelberts et al.(199)	2002	Carbamazepine in individuals with epilepsy vs. Healthy controls	Rey Auditory Verbal Learning Test Trial: *P* = NS Max: *P* = NS Delta: *P* = NS Total Recall: *P* = NS Delayed Recall: *P* = NS Stroop Test Card I: *P* < 0.008 Card II: *P* < 0.003 Card III: *P* = NS Interference: *P* = NS	Slower information processing was found for: • Stroop Test card I and II No problem with memory functioning was detected for: • Primary recall of new information • Long-term memory consolidation There was no evidence of difference in: • Selective attention functioning
Hessen et al.(200)	2006	AED discontinuation (carbamazepine or valproate) vs AED (carbamazepine or valproate) continuation	Simple RT *Dominant Hand* Patient: -2.75 Control: -13.38 *Nondominant Hand* Patient: 0.38 Control: 5.35 Choice RT Patient: -24.02 Control: 4.07 Sequential RT Patient: -9.28 Control: -17.69 Language discrimination Patient: -17.44	The main finding of the study was that AED discontinuation of major AEDs significantly improves performance on tests that require complex cognitive processing under time pressure, as in: • Divided attention • Rapid language discrimination • Rapid form discrimination There were statistically significant improvements for the discontinuation group in the following tests: • Choice Reaction Time • Language discrimination • Form discrimination There were no statistically significant improvements for the discontinuation group in the following tests:

Reference	Year	Comparison	Test and Findings	Conclusion
			Control: 6.99 Simple RT2 Patient: 1.94 Control: 2.19 Degraded Words distract ms Patient: -14.11 Control: 9.92 Response reversal ms Patient: -26.19 Control: -1.96 Form discrimination ms Patient: -34.98 Control: 8.07 Simple RT 3 Patient: 12.89 Control: 0.15	• Simple Reaction Time • Response reversal • Degraded words with distraction • Sequential reaction time

Hessen et al. reported that "function improved significantly more" among individuals who underwent AED discontinuation than among individuals who continued taking AEDs on three of the six complex tests, including choice reaction time, rapid language discrimination, and form discrimination. Rapid visual scanning was 'significantly better' in the discontinuation group when compared to the continuation group ($P = 0.0470$, and in degraded words with distraction, improvement in the discontinuation group was close to significant ($P = 0.067$). There was no difference between groups in the test of sequential reaction time, or in any of the tests of simple reaction time. The main finding of the study was that AED discontinuation 'significantly improves performance on tests that require complex cognitive processing under pressure, as in divided attention, rapid language discrimination, and rapid form discrimination'. The authors concluded that individuals with epilepsy who are seizure free might experience an improvement in cognitive function with the discontinuation of AED therapy.

Engelberts et al. reported that while the 'performance of the patients [individuals with epilepsy] was slower than that of healthy controls,' there was 'no impairment in selective attention, memory functioning, or executive functioning found.' These results contrasted with the findings of a previous study conducted and discussed by Engelberts et al., where deficits were found in each of these cognitive domains in individuals who experienced a maximum of one seizure a month, without restrictions on age at onset or epilepsy duration. In comparing the findings of these two studies, Engelberts et al. concluded that individuals with well-controlled epilepsy with an age at onset > 18 years old, a long duration of epilepsy, and are seizure free are a distinct category of individuals from those who experienced a maximum of one seizure a month, without restrictions on age at onset or epilepsy duration.

Section Summary

Cognitive and psychomotor deficits have been demonstrated in studies of AED use in individuals with epilepsy. However, FMCSA is interested in the relationship between AED use and cognitive and psychomotor deficits in a specific group of individuals who might qualify for a CMV driver's 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:

3. **A paucity of data precludes one from 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.

4. **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: 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 these 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) which 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 AEDs use, experienced improved performance on cognitive and psychomotor tests which required complex cognitive processing under pressure, including divided attention, rapid language discrimination, and rapid form discrimination when compared to 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 (CBZ or VPA). The authors go on to 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 there exist several differences 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.

Bibliography

1. Shadish WR, Haddock CK. Combining estimates of effect size. In: Cooper H, Hedges LV, editors. The handbook of research synthesis. New York (NY): Russell Sage Foundation; 1994. p. 261-77.
2. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998 Dec 30;17(24):2815-34.
3. Hedges LV. Fixed effects models. In: Cooper H, Hedges LV, editors. The handbook of research synthesis. New York (NY): Russell Sage Foundation; 1994. p. 285-99.
4. Raudenbush SW. Random effects models. In: Cooper H, Hedges LV, editors. The handbook of research synthesis. New York (NY): Russell Sage Foundation; 1994. p. 301-21.
5. Hedges LV, Vevea JL. Fixed- and random-effects models in meta-analysis. Psychol Methods 1998;3(4):486-504.
6. Gavaghan DJ, Moore RA, McQuay HJ. An evaluation of homogeneity tests in meta-analyses in pain using simulations of individual patient data. Pain 2000 Apr;85(3):415-24.
7. Takkouche B, Cadarso-Suarez C, Spiegelman D. Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. Am J Epidemiol 1999 Jul 15;150(2):206-15.
8. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002 Jun 15;21(11):1539-58.
9. Conti CR. Clinical decision making using cumulative meta-analysis [editorial]. Clin Cardiol 1993 Mar;16(3):167-8.
10. Mottola CA. Assessing and enhancing reliability. Decubitus 1992 Nov;5(6):42-4.
11. Sterne J. sbe22: Cumulative meta-analysis. Stata Technical Bulletin 1998;42:13-6.
12. Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. BMJ 2000 Jun 10;320(7249):1574-7.
13. Duval S, Tweedie R. Practical estimates of the effect of publication bias in meta-analysis. Australasian Epidemiologist 1998;5:14-7.
14. Duval SJ, Tweedie RL. A non-parametric 'trim and fill' method of assessing publication bias in meta-analysis. J Am Stat Assoc 2000 Mar;95(449):89-98.
15. American Epilepsy Society. Basic mechanisms underlying seizures and epilepsy. Hartford (CT): American Epilepsy Society; 2004 Sep. 17 p. Also available: http://www.aesnet.org/visitors/professionaldevelopment/meded/newppt/basic/BASICORE.PDFB.
16. American Epilepsy Society. Neuropharmacology of antiepileptic drugs. Hartford (CT): American Epilepsy Society; 2004 Sep 1. 28 p.
17. Berg A. The language of epilepsy: a guide to common terminology. [internet]. Hartford (CT): Connecticut Study of Epilepsy; [accessed 2007 Feb 6]. [3 p]. Available: http://www.ctstudyofepilepsy.info/pdfs/publication_language_of_epilepsy.pdf.
18. Pohlmann-Eden B, Beghi E, Camfield C, Camfield P. The first seizure and its management in adults and children. BMJ 2006 Feb 11;332(7537):339-42.
19. World Health Organization (WHO). Atlas: epilepsy care in the world. Geneva, Switzerland: World Health Organization (WHO); 2005. 91 p.
20. LaRoche SM, Helmers SL. The new antiepileptic drugs: scientific review. JAMA 2004 Feb 4;291(5):605-14.
21. Hesselbrock MN. Gender comparison of antisocial personality disorder and depression in alcoholism. Special Issue: Women and substance abuse. J Subst Abuse 1991;3(2):205-19.
22. American Epilepsy Society. Clinical epilepsy. Hartford (CT): American Epilepsy Society; 2004 Oct 1. 58 p. Also available: http://www.aesnet.org/visitors/professionaldevelopment/meded/newppt/clinical/clinicore.pdf.
23. Jenssen S, Gracely EJ, Sperling MR. How long do most seizures last? A systematic comparison of seizures recorded in the epilepsy monitoring unit. Epilepsia 2006;47(9):1499-503.

24. NINDS epilepsy information page. [internet]. Bethesda (MD): National Institute of Neurological Disorders and Stroke (NINDS); [accessed 2007 Mar 6]. [4 p]. Available: http://www.ninds.nih.gov/disorders/epilepsy/epilepsy.htm?css=print.

25. Hulihan JF. Reflex epilepsy. In: eMedicine [database online]. Omaha (NE): eMedicine.com, Inc.; 1996- [updated 2005 Nov 22]. [accessed 2007 Jan 25]. [5 p]. Available: http://www.emedicine.com/NEURO/topic687.htm.

26. Vignatelli L, Bisulli F, Naldi I, Ferioli S, Pittau F, Provini F, Plazzi G, Vetrugno R, Montagna P, Tinuper P. Excessive daytime sleepiness and subjective sleep quality in patients with nocturnal frontal lobe epilepsy: a case-control study. Epilepsia 2006;47 Suppl 5:73-7.

27. Ryvlin P, Rheims S, Risse G. Nocturnal frontal lobe epilepsy. Epilepsia 2006;47 Suppl 2:83-6.

28. Bazil CW. Nocturnal seizures. Semin Neurol 2004 Sep;24(3):293-300.

29. Stables JP, Bertram EH, White HS, Coulter DA, Dichter MA, Jacobs MP, Loscher W, Lowenstein DH, Moshe SL, Noebels JL, Davis M. Models for epilepsy and epileptogenesis: report from the NIH workshop, Bethesda, Maryland. Epilepsia 2002 Nov;43(11):1410-20.

30. Epilepsy and seizure statistics. [internet]. Landover (MD): Epilepsy Foundation; [accessed 2006 Jul 5]. [3 p]. Available: http://www.epilepsyfoundation.org/answerplace/statistics.cfm.

31. Sander JW. The incidence and prevalence of epilepsy. [internet]. Bucks (UK): National Society for Epilepsy (NSE); 2005 Oct [accessed 2006 Jul 5]. [6 p]. Available: http://www.e-epilepsy.org.uk/pages/articles/text.cfm?id=26.

32. Elan Pharma International Ltd. Zonegran (zonisamide) package insert [rev-3 ver-1]. Teaneck (NJ): Elan Pharma International Ltd.; 2004 Dec. 12 p.

33. Wyler AR. Recent advances in epilepsy surgery: temporal lobectomy and multiple subpial transections. Neurosurgery 1997 Dec;41(6):1294-301; discussion 1301.

34. National Institutes of Health Consensus Development Conference Statement: surgery for epilepsy, March 19-21, 1990. Epilepsia 1990 Nov-Dec;31(6):806-12.

35. Tatum WO 4th, Benbadis SR, Vale FL. The neurosurgical treatment of epilepsy. Arch Fam Med 2000 Nov-Dec;9(10):1142-7.

36. Wyler AR, Hermann BP, Somes G. Extent of medial temporal resection on outcome from anterior temporal lobectomy: a randomized prospective study. Neurosurgery 1995 Nov;37(5):982-90; discussion 990-1.

37. Olivier A. Surgical techniques in temporal lobe epilepsy. Clin Neurosurg 1997;44:211-41.

38. Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain 2005 May;128(Pt 5):1188-98.

39. Chapell R, Reston J, Snyder D, Treadwell J, Treager S, Turkelson C. Management of treatment-resistant epilepsy. Evid Rep Technol Assess (Summ) 2003 Apr;(77):1-8.

40. Engel J Jr, Wiebe S, French J, Sperling M, Williamson P, Spencer D, Gumnit R, Zahn C, Westbrook E, Enos B. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the AANS [trunc]. Neurology 2003 Feb 25;60(4):538-47.

41. Lesser RP, Fisher RS, Uematsu S. Assessment of surgical outcome. Epilepsy Res 1992;(Suppl 5):217-29.

42. Gates JR, Wada JA, Reeves AG, Lassonde M, Papo I, Spencer SS, Andermann F, Risse G, Ritter FJ, Purves SJ. Reevaluation of corpus callosotomy. In: Surgical treatment of the epilepsies. 2nd ed. New York (NY): Raven Press; 1993. p. 637-48.

43. Carson BS Sr. Indications and outcomes for lobectomy, corpus callosotomy, and hemispherectomy in pediatric neurosurgical patients. Clin Neurosurg 2000;47:385-99.

44. Gates JR, Rosenfeld WE, Maxwell RE, Lyons RE. Response of multiple seizure types to corpus callosum section. Epilepsia 1987 Jan-Feb;28(1):28-34.

45. Victor M, Ropper AH. Adams and Victor's principles of neurology. 7th ed. New York (NY): McGraw-Hill Companies, Inc.; 2001. Epilepsy and other seizure disorders. p. 331-65.

46. Vining EP, Freeman JM, Pillas DJ, Uematsu S, Carson BS, Brandt J, Boatman D, Pulsifer MB, Zuckerberg A. Why would you remove half a brain? The outcome of 58 children after hemispherectomy-the Johns Hopkins experience: 1968 to 1996. Pediatrics 1997 Aug;100(2 Pt 1):163-71.

47. Berg AT, Shinnar S. The contributions of epidemiology to the understanding of childhood seizures and epilepsy. J Child Neurol 1994 Oct;9(Suppl 2):19-26.

48. Tinuper P, Andermann F, Villemure JG, Rasmussen TB, Quesney LF. Functional hemispherectomy for treatment of epilepsy associated with hemiplegia: rationale, indications, results, and comparison with callosotomy. Ann Neurol 1988 Jul;24(1):27-34.

49. Morrell F, Whisler WW, Bleck TP. Multiple subpial transection: a new approach to the surgical treatment of focal epilepsy. J Neurosurg 1989 Feb;70(2):231-9.

50. Morrell F, Kanner AM, de Toledo-Morrell L, Hoeppner T, Whisler WW. Multiple subpial transection. Adv Neurol 1999;81:259-70.

51. Orbach D, Romanelli P, Devinsky O, Doyle W. Late seizure recurrence after multiple subpial transections. Epilepsia 2001;49(9):1130-33.

52. Mulligan LP, Spencer DD, Spencer SS. Multiple subpial transections: the Yale experience. Epilepsia 2001 Feb;42(2):226-9.

53. Sawhney IM, Robertson IJ, Polkey CE, Binnie CD, Elwes RD. Multiple subpial transection: a review of 21 cases. J Neurol Neurosurg Psychiatry 1995 Mar;58(3):344-9.

54. Begley CE, Famulari M, Annegers JF, Lairson DR, Reynolds TF, Coan S, Dubinsky S, Newmark ME, Leibson C, So EL, Rocca WA. The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. Epilepsia 2000 Mar;41(3):342-51.

55. Ikuma E. Driving with insulin-treated diabetes. Honolulu (HI): Legislative Reference Bureau; 2002 Dec. 43 p. Also available: http://www.hawaii.gov/lrb.

56. Krauss GL, Ampaw L, Krumholz A. Individual state driving restrictions for people with epilepsy in the US. Neurology 2001 Nov 27;57(10):1780-5.

57. Treadwell JT, Tregear SJ, Reston JT, Turkelson CM. A system for rating the stability and strength of medical evidence. BMC Med Res Methodol 2006 Oct 19;6:52. Also available: http://www.biomedcentral.com/1471-2288/6/52.

58. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993 Jul-Aug;34(4):592-6.

59. Vermeulen J, Aldenkamp AP. Cognitive side-effects of chronic antiepileptic drug treatment: a review of 25 years of research. Epilepsy Res 1995 Oct;22(2):65-95.

60. Dodrill CB. Problems in the assessment of cognitive effects of antiepileptic drugs. Epilepsia 1992;33 Suppl 6:S29-32.

61. Sutton AJ, Abrams KR, Jones DR, Sheldon T, Song F, editors. Methods for meta-analysis in medical research. John Wiley & Sons; 2001 Jan. 274 p. (Wiley series in probability and mathematical statistics;)..

62. Fleiss JL. Measures of effect size for categorical data. In: Cooper H, Hedges LV, editors. The handbook of research synthesis. New York: Russell Sage Foundation; 1994. p. 245-60.

63. Greenhouse JB, Iyengar S. Sensitivity analysis and diagnostics. In: Cooper H, Hedges LV, editors. The handbook of research synthesis. New York: Russell Sage Foundation; 1994. p. 383-409.

64. Petitti DB. Approaches to heterogeneity in meta-analysis. Stat Med 2001 Dec 15;20(23):3625-33.

65. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 6;327(7414):557-60.

66. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002 Feb 28;21(4):589-624.

67. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med 2002 Jun 15;21(11):1559-73.

68. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. Stat Med 2004 Jun 15;23(11):1663-82.

69. Olkin I. Diagnostic statistical procedures in medical meta-analysis. Stat Med 1999 Sep 15;18(17-18):2331-41.

70. Lau J, Schmid CH, Chalmers TC. Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. J Clin Epidemiol 1995 Jan;48(1):45-57; 59-60.

71. Ioannidis JP, Contopoulos-Ioannidis DG, Lau J. Recursive cumulative meta-analysis: a diagnostic for the evolution of total randomized evidence from group and individual patient data. J Clin Epidemiol 1999 Apr;52(4):281-91.

72. Ioannidis J, Lau J. Evolution of treatment effects over time: empirical insight from recursive cumulative meta-analyses. Proc Natl Acad Sci U S A 2001;98:831-6.

73. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000 Jun;56(2):455-63.

74. Cooper H, Hedges LV, editors. The handbook of research synthesis. New York (NY): Russell Sage Foundation; 1994. 573 p.

75. Shore T, Nelson N, Weinerman B. A meta-analysis of stages I and II Hodgkin's disease. Cancer 1990 Mar 1;65(5):1155-60.

76. Earle CC, Pham B, Wells GA. An assessment of methods to combine published survival curves. Med Decis Making 2000 Jan-Mar;20(1):104-11.

77. Charlton J, Koppel S, O'Hare M, Andrea D, Smith G, Khodr B, Langford J, Odell M, Fildes B. Influence of chronic illness on crash involvement of motor vehicle drivers. Victoria, Autralia: Monash University, Accident Research Centre; 2004 Apr. (Report; no. 213).

78. Tomson T, Beghi E, Sundqvist A, Johannessen SI. Medical risks in epilepsy: a review with focus on physical injuries, mortality, traffic accidents and their prevention. Epilepsy Res 2004 Jun;60(1):1-16.

79. Remillard GM, Zifkin BG, Andermann F. Epilepsy and motor vehicle driving--a symposium held in Quebec City, November 1998. Can J Neurol Sci 2002 Nov;29(4):315-25.

80. Hansotia P. Automobile driving and epilepsy: a medical perspective. Wis Med J 1991 Mar;90(3):112-5.

81. Krumholz A, Fisher RS, Lesser RP, Hauser WA. Driving and epilepsy. A review and reappraisal. JAMA 1991 Feb 6;265(5):622-6.

82. Yale SH, Hansotia P, Knapp D, Ehrfurth J. Neurologic conditions: assessing medical fitness to drive. Clin Med Res 2003 Jul;1(3):177-88.

83. National Highway Traffic Safety Administration. Medical conditions and driving: a review of the scientific literature (1960-2000). Washington (DC): U.S. Department of Transportation, National Highway Traffic Safety Administration; 2005 Sep. 162 p. Also available: http://www.nhtsa.dot.gov/people/injury/research/Medical%5FCondition%5FDriving/Medical%20Cond%20809%20690-8-04_Medical%20Cond%20809%20690-8-04.pdf.

84. Sheth SG, Krauss G, Krumholz A, Li G. Mortality in epilepsy: driving fatalities vs other causes of death in patients with epilepsy. Neurology 2004 Sep 28;63(6):1002-7.

85. Vernon DD, Diller EM, Cook LJ, Reading JC, Suruda AJ, Dean JM. Evaluating the crash and citation rates of Utah drivers licensed with medical conditions, 1992-1996. Accid Anal Prev 2002 Mar;34(2):237-46.

86. Lings S. Increased driving accident frequency in Danish patients with epilepsy. Neurology 2001 Aug 14;57(3):435-9.

87. Taylor J, Chadwick D, Johnson T. Risk of accidents in drivers with epilepsy. J Neurol Neurosurg Psychiatry 1996 Jun;60(6):621-7.

88. Hansotia P, Broste SK. The effect of epilepsy or diabetes mellitus on the risk of automobile accidents. N Engl J Med 1991 Jan 3;324(1):22-6.

89. Popkin CL, Waller PF. Epilepsy and driving in North Carolina: an exploratory study. Accid Anal Prev 1989 Aug;21(4):389-93.

90. Davis TG, Wehling EH, Carpenter RL. Oklahoma's medically restricted drivers. A study of selected medical conditions. J Okla State Med Assoc 1973 Jul;66(7):322-7.

91. McMurray L, Crancer A Jr. Accident and violation rates of Washington's medically restricted drivers. JAMA 1968;205:272-6.

92. Waller JA. Chronic medical conditions and traffic safety: review of the California experience. N Engl J Med 1965 Dec 23;273(26):1413-20.

93. Mueller MJ. Identifying patients with diabetes mellitus who are at risk for lower-extremity complications: use of Semmes-Weinstein monofilaments. Phys Ther 1996 Jan;76(1):68-71.

94. Krauss GL, Krumholz A, Carter RC, Li G, Kaplan P. Risk factors for seizure-related motor vehicle crashes in patients with epilepsy. Neurology 1999 Apr 22;52(7):1324-9.

95. Gastaut H, Zifkin BG. The risk of automobile accidents with seizures occurring while driving: relation to seizure type. Neurology 1987 Oct;37(10):1613-6.

96. Sander JW. The natural history of epilepsy in the era of new antiepileptic drugs and surgical treatment. Epilepsia 2003;44 Suppl 1:17-20.

97. Kwan P, Sander JW. The natural history of epilepsy: an epidemiological view. J Neurol Neurosurg Psychiatry 2004 Oct;75(10):1376-81.

98. Marson AG, Williamson PR, Taylor S, Maguire M, Chadwick DW. Efficacy of carbamazepine and valproate as monotherapy for early epilepsy and single seizures. Neurology 2006 Nov 28;67(10):1872-5.

99. Blum DE. New drugs for persons with epilepsy. Adv Neurol 1998;76:57-87.

100. Brodie MJ, French JA. Management of epilepsy in adolescents and adults. Lancet 2000 Jul 22;356(9226):323-9.

101. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000 Feb 3;342(5):314-9.

102. Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. Lancet 2006 Apr 1;367(9516):1087-100.

103. Cockerell OC, Johnson AL, Sander JW, Hart YM, Shorvon SD. Remission of epilepsy: results from the National General Practice Study of Epilepsy. Lancet 1995 Jul 15;346(8968):140-4.

104. Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. Epilepsia 1979 Dec;20(6):729-37.

105. Aktekin B, Dogan EA, Oguz Y, Senol Y. Withdrawal of antiepileptic drugs in adult patients free of seizures for 4 years: a prospective study. Epilepsy Behav 2006 May;8(3):616-9.

106. Sillanpaa M, Schmidt D. Prognosis of seizure recurrence after stopping antiepileptic drugs in seizure-free patients: A long-term population-based study of childhood-onset epilepsy. Epilepsy Behav 2006 Jun;8(4):713-9.

107. Kalita J, Vajpeyee A, Misra UK. Predictors of one-year seizure remission--a clinicoradiological and electroencephalographic study. Electromyogr Clin Neurophysiol 2005 Apr-May;45(3):161-6.

108. Cardoso TA, Cendes F, Guerreiro CA. Is low antiepileptic drug dose effective in long-term seizure-free patients. Arq Neuropsiquiatr 2003 Sep;61(3A):566-73.

109. Specchio LM, Tramacere L, La Neve A, Beghi E. Discontinuing antiepileptic drugs in patients who are seizure free on monotherapy. J Neurol Neurosurg Psychiatry 2002 Jan;72(1):22-5.

110. Lossius MI, Stavem K, Gjerstad L. Predictors for recurrence of epileptic seizures in a general epilepsy population. Seizure 1999 Dec;8(8):476-9.

111. 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.

112. Anonymous. Practice parameter: A guideline for discontinuing antiepileptic drugs in seizure-free patients - Summary statement. Neurology 1996;47(2):600-2.

113. Nakazawa Y, Ishida S, Maeda H, Sakurai S, Motooka H. Prognosis of epilepsy withdrawn from antiepileptic drugs. Psychiatry Clin Neurosci 1995 Jun;49(3):163-8.

114. Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. Neurology 1994 Apr;44(4):601-8.

115. Mukasa H, Ueda S, Ishida S, Maeda H, Nakazawa Y. A long-term follow-up and clinical study of epileptics whose medication was terminated. Jpn J Psychiatry Neurol 1994 Jun;48(2):259-63.

116. Medical Research Council Antiepileptic Drug Withdrawal Study Group. Prognostic index for recurrence of seizures after remission of epilepsy. BMJ 1993 May 22;306(6889):1374-8.

117. Tanaka H, Takeda A, Okada H, Izumi M, Ishikawa S. Long-term effectiveness of antiepileptic drug treatment and seizure recurrence in patients with epilepsy. Jpn J Psychiatry Neurol 1992 Jun;46(2):424-6.

118. Medical Research Council Antiepileptic Drug Withdrawal Study Group. Randomised study of antiepileptic drug withdrawal in patients in remission. Lancet 1991 May 18;337(8751):1175-80.

119. Callaghan N, Garrett A, Goggin T. Withdrawal of anticonvulsant drugs in patients free of seizures for two years. A prospective study. N Engl J Med 1988 Apr 14;318(15):942-6.

120. Beghi E, Collaborative Group for the Study of Epilepsy, Tognoni G. Prognosis of epilepsy in newly referred patients: a multicenter prospective study. Epilepsia 1988 May-Jun;29(3):236-43.

121. Chadwick D. Starting and stopping treatment for seizures and epilepsy. Epilepsia 2006;47 Suppl 1:58-61.

122. So EL, Radhakrishnan K, Silbert PL, Cascino GD, Sharbrough FW, O'Brien PC. Assessing changes over time in temporal lobectomy: outcome by scoring seizure frequency. Epilepsy Res 1997 May;27(2):119-25.

123. Salanova V, Markand O, Worth R. Longitudinal follow-up in 145 patients with medically refractory temporal lobe epilepsy treated surgically between 1984 and 1995. Epilepsia 1999 Oct;40(10):1417-23.

124. Foldvary N, Nashold B, Mascha E, Thompson EA, Lee N, McNamara JO, Lewis DV, Luther JS, Friedman AH, Radtke RA. Seizure outcome after temporal lobectomy for temporal lobe epilepsy: a Kaplan-Meier survival analysis. Neurology 2000 Feb 8;54(3):630-4.

125. Radhakrishnan K, So EL, Silbert PL, Jack CR, Cascino GD, Sharbrough FW, O'Brien PC. Predictors of outcome of anterior temporal lobectomy for intractable epilepsy: a multivariate study. Neurology 1998 Aug;51(2):465-71.

126. Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, Shinnar S, Langfitt JT, Walczak TS, Pacia SV, Multicenter Study of Epilepsy Surgery. Predicting long-term seizure outcome after resective epilepsy surgery: the multicenter study. Neurology 2005 Sep 27;65(6):912-8.

127. Kim YD, Heo K, Park SC, Huh K, Chang JW, Choi JU, Chung SS, Lee BI. Antiepileptic drug withdrawal after successful surgery for intractable temporal lobe epilepsy. Epilepsia 2005 Feb;46(2):251-7.

128. Jeha LE, Najm IM, Bingaman WE, Khandwala F, Widdess-Walsh P, Morris HH, Dinner DS, Nair D, Foldvary-Schaeffer N, Prayson RA, Comair Y, O'Brien R, Bulacio J, Gupta A, Luders HO. Predictors of outcome after temporal lobectomy for the treatment of intractable epilepsy. Neurology 2006 Jun 27;66(12):1938-40.

129. Kelley K, Theodore WH. Prognosis 30 years after temporal lobectomy. Neurology 2005 Jun 14;64(11):1974-6.

130. McIntosh AM, Kalnins RM, Mitchell LA, Fabinyi GC, Briellmann RS, Berkovic SF. Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. Brain 2004 Sep;127(Pt 9):2018-30.

131. Yoon HH, Kwon HL, Mattson RH, Spencer DD, Spencer SS. Long-term seizure outcome in patients initially seizure-free after resective epilepsy surgery. Neurology 2003 Aug 26;61(4):445-50.

132. Jutila L, Immonen A, Mervaala E, Partanen J, Partanen K, Puranen M, Kalviainen R, Alafuzoff I, Hurskainen H, Vapalahti M, Ylinen A. Long term outcome of temporal lobe epilepsy surgery: analyses of 140 consecutive patients. J Neurol Neurosurg Psychiatry 2002 Nov;73(5):486-94.

133. Eliashiv SD, Dewar S, Wainwright I, Engel J, Fried I. Long-term follow-up after temporal lobe resection for lesions associated with chronic seizures. Neurology 1997 May;48(5):1383-8.

134. Luders H, Murphy D, Awad I, Wyllie E, Dinner DS, Morris HH 3rd, Rothner AD. Quantitative analysis of seizure frequency 1 week and 6, 12, and 24 months after surgery of epilepsy. Epilepsia 1994 Nov-Dec;35(6):1174-8.

135. Rougier A, Dartigues JF, Commenges D, Claverie B, Loiseau P, Cohadon F. A longitudinal assessment of seizure outcome and overall benefit from 100 cortectomies for epilepsy. J Neurol Neurosurg Psychiatry 1992 Sep;55(9):762-7.

136. Burneo JG, Knowlton RC, Martin R, Faught RE, Kuzniecky RI. Race/ethnicity: a predictor of temporal lobe epilepsy surgery outcome. Epilepsy Behav 2005 Nov;7(3):486-90.

137. Stavem K, Bjornaes H, Langmoen IA. Predictors of seizure outcome after temporal lobectomy for intractable epilepsy. Acta Neurol Scand 2004 Apr;109(4):244-9.

138. Salanova V, Markand O, Worth R. Temporal lobe epilepsy surgery: outcome, complications, and late mortality rate in 215 patients. Epilepsia 2002 Feb;43(2):170-4.

139. Kilpatrick C, Cook M, Matkovic Z, O'Brien T, Kaye A, Murphy M. Seizure frequency and duration of epilepsy are not risk factors for postoperative seizure outcome in patients with hippocampal sclerosis. Epilepsia 1999 Jul;40(7):899-903.

140. 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.

141. Berg AT, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. Neurology 1991 Jul;41(7):965-72.

142. Hauser WA, Lee JR. Do seizures beget seizures. Prog Brain Res 2002;135:215-9.

143. 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.

144. 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.

145. Kotsopoulos I, de Krom M, Kessels F, Lodder J, Troost J, Twellaar M, van Merode T, Knottnerus A. Incidence of epilepsy and predictive factors of epileptic and non-epileptic seizures. Seizure 2005 Apr;14(3):175-82.

146. Madhusudanan M. First unprovoked seizure--to treat or not to treat. J Assoc Physicians India 2000 May;48(5):519-24.

147. Beghi E, First Seizure Trial Group, Ciccone A. 3Recurrence after a first unprovoked seizure. Is it still a controversial issue? Seizure 1993 Mar;2(1):5-10.

148. 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.

149. Van Donselaar CA, Geerts AT, Schimsheimer R-J. Idiopathic first seizure in adult life: Who should be treated? BMJ 1991;302(6777):620-3.

150. van Donselaar CA, Geerts AT, Schimsheimer RJ. Idiopathic first seizure in adult life: who should be treated? BMJ 1991 Mar 16;302(6777):620-3.

151. Wagner ML, Murad D, Patel D. Compliance in epilepsy: a review. In: U.S. Pharmacist Online [internet]. Jobson Medical Information LLC[accessed 2007 Jan 25]. [8 p]. Available: http://www.uspharmacist.com/oldformat.asp?url=newlook/files/feat/acf4a7b.htm.

152. Garnett WR. Antiepileptic drug treatment: outcomes and adherence. Pharmacotherapy 2000 Aug;20(8 Pt 2):191S-199S.

153. Martin R, Vogtle L, Gilliam F, Faught E. What are the concerns of older adults living with epilepsy. Epilepsy Behav 2005 Sep;7(2):297-300.

154. Krueger KP, Felkey BG, Berger BA. Improving adherence and persistence: a review and assessment of interventions and description of steps toward a national adherence initiative. J Am Pharm Assoc (Wash DC) 2003 Nov-Dec;43(6):668-78; quiz 678-9.

155. Leppik IE. How to get patients with epilepsy to take their medication. The problem of noncompliance. Postgrad Med 1990 Jul;88(1):253-6.

156. Peterson GM, McLean S, Millingen KS. Determinants of patient compliance with anticonvulsant therapy. Epilepsia 1982 Dec;23(6):607-13.

157. Long L, Reeves AL, Moore JL, Roach J, Pickering CT. An assessment of epilepsy patients' knowledge of their disorder. Epilepsia 2000 Jun;41(6):727-31.

158. Schmidt D, Reininghaus R, Winkel R. Relevance of poor compliance for seizure control. In: Schmidt D, Leppik IE, editors. Compliance in epilepsy (Epilepsy Res Suppl 1). Amsterdam: Elsevier Science; 1988. p. 141-6.

159. Liu L, Yiu CH, Yen DJ, Chou MH, Lin MF. Medication education for patients with epilepsy in Taiwan. Seizure 2003 Oct;12(7):473-7.

160. Krueger KP, Berger BA, Felkey B. Medication adherence and persistence: a comprehensive review. Adv Ther 2005 Jul-Aug;22(4):313-56.

161. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. JAMA 1989 Jun 9;261(22):3273-7.

162. Peytchev L. Therapeutic drug monitoring of anticonvulsants in epilepsy. Period Biol 1997;99(4):493-7.

163. Stanaway L, Johnson RH, Lambie DG. Epilepsy and driving. N Z Med J 1983;96(735):525-8.

164. Williams J, Myson V, Steward S, Jones G, Wilson JF, Kerr MP, Smith PE. Self-discontinuation of antiepileptic medication in pregnancy: detection by hair analysis. Epilepsia 2002 Aug;43(8):824-31.

165. Williams J, Patsalos PN, Wilson JF. Hair analysis as a potential index of therapeutic compliance in the treatment of epilepsy. Forensic Sci Int 1997 Jan 17;84(1-3):113-22.

166. Perucca E, Meador KJ. Adverse effects of antiepileptic drugs. Acta Neurol Scand Suppl 2005;181:30-5.

167. Leppik IE, Cloyd JC, Sawchuck RJ, Pepin SM. Compliance and variability of plasma phenyloin levels in epileptic patients. Ther Drug Monit 1979;:475-83.

168. Chandra RS, Dalvi SS, Karnad PD, Kshirsagar NA, Shah PU. Compliance monitoring in epileptic patients. J Assoc Physicians India 1993 Jul;41(7):431-2.

169. Specht U, Elsner H, May TW, Schimichowski B, Thorbecke R. Post-ictal serum levels of antiepileptic drugs for detection of noncompliance. Epilepsy Behav 2003 Oct;4(5):487-95.

170. Kemp S, Feely M, Hay A, Wild H, Cooper C. Psychological factors and use of antiepileptic drugs: pilot work using an objective measure of adherence. Psychol Health Med 2007 Jan 1;12(1):107-13.

171. DiIorio C, Faherty B, Manteuffel B. Cognitive-perceptual factors associated with antiepileptic medication compliance. Res Nurs Health 1991 Oct;14(5):329-38.

172. Peterson GM, McLean S, Millingen KS. A randomised trial of strategies to improve patient compliance with anticonvulsant therapy. Epilepsia 1984 Aug;25(4):412-7.

173. Wannamaker BB, Morton WA Jr, Gross AJ, Saunders S. Improvement in antiepileptic drug levels following reduction of intervals between clinic visits. Epilepsia 1980 Apr;21(2):155-62.

174. Drane DL, Meador KJ. Cognitive and behavioral effects of antiepileptic drugs. Epilepsy Behav 2002 Oct;3(5S):49-53.

175. Loring DW, Meador KJ. Cognitive and behavioral effects of epilepsy treatment. Epilepsia 2001;42(Suppl 8):24-32.

176. Gates JR. Side Effect Profiles and Behavioral Consequences of Antiepileptic Medications. Epilepsy Behav 2000 Jun;1(3):153-159.

177. Greenwood RS. Adverse effects of antiepileptic drugs. Epilepsia 2000;41 Suppl 2:S42-52.

178. McKnight AJ, McKnight AS. Multivariate analysis of age-related driver ability and performance deficits. Accid Anal Prev 1999 Sep;31(5):445-54.

179. Hindmarch I, Trick L, Ridout F. A double-blind, placebo- and positive-internal-controlled (alprazolam) investigation of the cognitive and psychomotor profile of pregabalin in healthy volunteers. Psychopharmacology 2005;183(2):133-43.

180. Kay GG. Measuring impairment: validated test methods for assessing sedating medications. [slide show online]. Washington (DC): U.S. Food and Drug Administration; 2001 Nov 14-15 [accessed 2006 Sep 22]. [17 slides]. Available: http://www.fda.gov/ohrms/dockets/dockets/01n0397/ts00001/tsld001.htm.

181. Fulda S, Schulz H. Cognitive dysfunction in sleep disorders. Sleep Med Rev 2001 Dec;5(6):423-445.

182. Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, Mason A, Golder S, O'Meara S, Sculpher M, Drummond M, Forbes C. Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation. London: National Institute for Health and Clinical Excellence (NICE);

2005 Apr 1. Appendix 5: details of cognitive measures used in RCTs. (Health Technology Assessment; vol. 9, no. 15). p. 183-185.

183. Sumer N, Ayvasik HB, Er N. Cognitive and psychomotor correlates of self-reported driving skills and behavior. In: Proceedings of the Third International Driving Symposium on Human Factors in Driving Assessment, Training and Vehicle Design. June 27-30, 2005; Rockport (ME). 2005. 8 p. Also available: http://ppc.uiowa.edu/driving-assessment/2005/final/papers/14_NebiSumerformat.pdf.

184. Roth T, Roehrs TA, Moskowitz H. Issues in drug-related performance impairment. Clin Ther 1992 Sep-Oct;14(5):654-66; discussion 653.

185. Engum ES, Cron L, Hulse CK, Pendergrass TM, Lambert W. Cognitive behavioral driver's inventory. Cogn Rehabil 1988;:35-49.

186. Vaa T. Impairments, diseases, age and their relative risks of accident involvement: results from meta-analysis. (Prepared under Contract no. GMA1/2000/2703 SI2.319837). [IMMORTAL Deliverable R1.1]. Vienna: Austrian Road Safety Board; 2003 Aug 30. 51 p. Also available: http://www.immortal.or.at.

187. Irving A, Jones W. Methods for testing impairment of driving due to drugs. Eur J Clin Pharmacol 1992;43(1):61-6.

188. Wingen M, Anderson HF, Borthmer J, Langer S, Ramaeers JG. Driving performance, psychomotor performance and cognitive function in healthy subjects: a comparison of escitalopram versus mirtazapine and placebo. P.1.072. [internet]. Stockholm: 17th Congress of the European College of Neuropharmacology; 2004 [accessed 2006 Sep 22]. [1 p]. Available: http://www-np.unimaas.nl/psypharm/Wingen_escit.pdf.

189. Laboratory. [internet]. Netherlands: University of Maastricht; 2005 Aug 25 [accessed 2006 Sep 8]. [2 p]. Available: http://www-np.unimaas.nl/psypharm/laboratory.htm.

190. Reger MA, Welsh RK, Watson GS, Cholerton B, Baker LD, Craft S. The relationship between neuropsychological functioning and driving ability in dementia: a meta-analysis. Neuropsychology 2004 Jan;18(1):85-93.

191. Muller W, Lautenschlager J. [Generalized tendomyopathy. I: Clinical aspects, follow-up and differential diagnosis]. Z Rheumatol 1990 Jan-Feb;49(1):11-21. (Ger).

192. Aldenkamp AP, Bodde N. Behaviour, cognition and epilepsy. Acta Neurol Scand Suppl 2005;182:19-25.

193. Ortinski P, Meador KJ. Cognitive side effects of antiepileptic drugs. Epilepsy Behav 2004 Feb;5 Suppl 1:S60-5.

194. Meador KJ, Gilliam FG, Kanner AM, Pellock JM. Cognitive and behavioral effects of antiepileptic drugs. Epilepsy Behav 2001 Aug;2(4):SS1-SS17.

195. Gallassi R, Morreale A, Lorusso S, Procaccianti G, Lugaresi E, Baruzzi A. Cognitive effects of valproate. Epilepsy Res 1990 Mar;5(2):160-4.

196. Meador KJ. Current discoveries on the cognitive effects of antiepileptic drugs. Pharmacotherapy 2000 Aug;20(8 Pt 2):185S-190S.

197. Zaccara G, Cincotta M, Borgheresi A, Balestrieri F. Adverse motor effects induced by antiepileptic drugs. Epileptic Disord 2004 Sep;6(3):153-68.

198. Dodrill CB. Effects of antiepileptic drugs on abilities. J Clin Psychiatry 1988 Apr;49 Suppl:31-4.

199. Engelberts NH, Klein M, van der Ploeg HM, Heimans JJ, Jolles J, Kasteleijn-Nolst Trenite DG. Cognition and health-related quality of life in chronic well-controlled patients with partial epilepsy on carbamazepine monotherapy. Epilepsy Behav 2002;3(4):316-21.

200. Hessen E, Lossius MI, Reinvang I, Gjerstad L. Influence of major antiepileptic drugs on attention, reaction time, and speed of information processing: results from a randomized, double-blind, placebo-controlled withdrawal study of seizure-free epilepsy patients receiving monotherapy. Epilepsia 2006 Dec;47(12):2038-45.

201. Barcs G, Vitrai J, Halasz P. Investigation of vehicle driving ability in two diagnostic groups of epileptic patients with special neuropsychological approach. Med Law 1997;16(2):277-87.

202. Beaussart M, Beaussart-Defaye J, Lamiaux JM, Grubar JC. Epileptic drivers--a study of 1,089 patients. Med Law 1997;16(2):295-306.

203. Beghi E, Cornaggia C, RESt-1 Group.. Morbidity and accidents in patients with epilepsy: results of a European cohort study. Epilepsia 2002 Sep;43(9):1076-83.

204. Bener A, Murdoch JC, Achan NV, Karama AH, Sztriha L. The effect of epilepsy on road traffic accidents and casualties. Seizure 1996 Sep;5(3):215-9.

205. Dixit SN, Jain S, Padma MV, Maheshwari MC. Gabapentin in refractory partial epilepsy - a trial in India. Acta Neurol Scand 1996;93(2-3):85-7.

206. Cimbura G, Lucas DM, Bennett RC, Warren RA, Simpson HM. Incidence and toxicological aspects of drugs detected in 484 fatally injured drivers and pedestrians in Ontario. J Forensic Sci 1982 Oct;27(4):855-67.

207. Constantinou JE, Gubbay SS. Epileptic seizures at the wheel: an 11-year experience. J Epilepsy 1990;3(4):201-5.

208. Drazkowski JF, Fisher RS, Sirven JI, Demaerschalk BM, Uber-Zak L, Hentz JG, Labiner D. Seizure-related motor vehicle crashes in Arizona before and after reducing the driving restriction from 12 to 3 months. Mayo Clin Proc 2003 Jul;78(7):819-25.

209. Fries M, Bickenbach J, Beckers S, Reinartz B, Rossaint R, Kunitz O. Neurological emergencies as causes of accidents. Eur J Emerg Med 2005 Aug;12(4):151-4.

210. Hansotia P, Broste SK. Epilepsy and traffic safety. Epilepsia 1993 Sep-Oct;34(5):852-8.

211. Hasegawa S, Kumagai K, Kaji S. Epilepsy and driving: a survey of automobile accidents attributed to seizure. Jpn J Psychiatry Neurol 1991 Jun;45(2):327-31.

212. Hashimoto K, Fukushima Y, Saito F, Wada K. A study on driving status in 98 epileptic patients with driving licences. Jpn J Psychiatry Neurol 1991 Jun;45(2):323-6.

213. Hierons R. The epileptic driver. Br Med J 1956 Jan 28;(4960):206-7.

214. Hormia. Does epilepsy mean a higher susceptibility to traffic accidents? Acta Psychiatr Scand 1961;36(Suppl 150):210-2.

215. Kugler J, Hiedl A, Spatz R. Sleep deprivation, epilepsy and the ability to operate a motor vehicle. Epilepsy Res Suppl 1991;2:261-4.

216. Lennox WG. Epilepsy and the epileptic; guest editorial. JAMA 1956 Sep 8;162(2):118-9.

217. McGlone R, Pritty P. Measuring anti-convulsant levels in the accident and emergency department. Arch Emerg Med 1986 Jun;3(2):141-3.

218. Millingen KS. Epilepsy and driving. Proc Aust Assoc Neurol 1976;13:67-72.

219. Norman LG. Medical aspects of road safety. Lancet 1960 May 7;1:989-94.

220. Parsons M. Fits and other causes of loss of consciousness while driving. Q J M 1986 Mar;58(227):295-303.

221. Rajna P, Solyom A, Mezofi L, Vargyai E, Kozma L, Tariska P. Car drivers with epilepsy (Pilot Hungarian EPIMED Database Evaluation). Epilepsy Behav 2003 Dec;4(6):761-3.

222. Seneviratne SL, Gunatilake SB, Adhikari AA, De Silva HJ. Driving and epilepsy in Sri Lanka. Seizure 1998 Aug;7(4):305-8.

223. Spudis EV, Penry JK, Gibson P. Driving impairment caused by episodic brain dysfunction. Restrictions for epilepsy and syncope. Arch Neurol 1986 Jun;43(6):558-64.

224. Takeda A, Kawai I, Fukushima Y, Yagi K. Driving and epilepsy: a prospective questionnaire survey in Japan. Committee on Driver's Licenses, the Japan Epilepsy Society, Shizuoka. Jpn J Psychiatry Neurol 1991 Jun;45(2):319-22.

225. Takeda A, Kawai I, Fukushima Y, Yagi K, Seino M. Epilepsy and driving in Japan: current status as investigated in a prospective survey. J Epilepsy 1992;5(2):135-9.

226. Taylor J, Chadwick DW, Johnson T. Accident experience and notification rates in people with recent seizures, epilepsy or undiagnosed episodes of loss of consciousness. QJM 1995 Oct;88(10):733-40.

227. Tiamkao S, Amornsin O, Pongchaiyakul C, Asawavichienjinda T, Yaudnopakao P, Jitpimolmard S, Arunpongpaisal S, Phuttharak W, Aaauevitchayapat N, Vannaprasaht S, Tiamkao S, Phunikhom K, Chaiyakum A, Saengsuwan J, Saetang S. Seizure-related injuries in northeast Thailand. J Med Assoc Thai 2006;89(5):608-13.

228. Kasteleijn-Nolst Trenite DG, Riemersma JB, Binnie CD, Smit AM, Meinardi H. The influence of subclinical epileptiform EEG discharges on driving behaviour. Electroencephalogr Clin Neurophysiol 1987 Aug;67(2):167-70.

229. van den Broek M, Beghi E, RESt-1 Group.. Accidents in patients with epilepsy: types, circumstances, and complications: a European cohort study. Epilepsia 2004 Jun;45(6):667-72.

230. van der Lugt PJ. Traffic accidents caused by epilepsy. Epilepsia 1975 Dec;16(5):747-51.

231. Wick JY, Zanni GR. Stranded: driving privileges revoked. Consult Pharm 2004;19(10):962-5.

232. Annegers JF, Hauser WA, Lee JR, Rocca WA. Incidence of acute symptomatic seizures in Rochester, Minnesota, 1935-1984. Epilepsia 1995 Apr;36(4):327-33.

233. Anonymous. When and how to withdraw anticonvulsants in seizure-free patients. Drugs Ther Perspect 1997;10(2):6-10.

234. Baumhackl U, Billeth R, Graf M. Type-specific diagnostic analysis of first epileptic seizure in adults. Eur Neurol 1994;34 Suppl 1:71-3.

235. Bazil CW. Comprehensive care of the epilepsy patient--control, comorbidity, and cost. Epilepsia 2004;45 Suppl 6:3-12.

236. Britton JW. Antiepileptic drug withdrawal: literature review. Mayo Clin Proc 2002 Dec;77(12):1378-88.

237. Chadwick D. Does withdrawal of different antiepileptic drugs have different effects on seizure recurrence? Further results from the MRC Antiepileptic Drug Withdrawal Study. Brain 1999 Mar;122 ((Pt 3)):441-8.

238. Chadwick D, Scherokman B. Randomised study of antiepileptic drug withdrawal in patients in remission. Ann Intern Med 1991;115(6 Suppl 2):39.

239. Davis R, Peters DH, McTavish D. Valproic acid. A reappraisal of its pharmacological properties and clinical efficacy in epilepsy. Drugs 1994 Feb;47(2):332-72.

240. Dichter MA. Deciding to discontinue antiepileptic medication. Hosp Pract (Off Ed) 1992;27(10A)

241. Hauser WA. Seizure disorders: the changes with age. Epilepsia 1992;33 Suppl 4:S6-14.

242. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia 1993 May-Jun;34(3):453-68.

243. Keranen T, Riekkinen PJ. Remission of seizures in untreated epilepsy. BMJ 1993 Aug 21;307(6902):483.

244. Kilpatrick CJ. Withdrawal of antiepileptic drugs in seizure-free adults. Aust Prescr 2004;27(5):114-7.

245. Kim JH. Pathology of seizure disorders. Neuroimaging Clin N Am 1995 Nov;5(4):527-45.

246. Lamdhade SJ, Taori GM. Study of factors responsible for recurrence of seizures in controlled epileptics for more than 1 years after withdrawal of antiepileptic drugs. Neurol India 2002 Sep;50(3):295-300.

247. Leppik I, De Rue K, Edrich P, Perucca E. Measurement of seizure freedom in adjunctive therapy studies in refractory partial epilepsy: the levetiracetam experience. Epileptic Disord 2006 Jun;8(2):118-30.

248. Lhatoo SD, Sander = JWAS, Shorvon SD. 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. J Neurol Neurosurg Psychiatry 2001;71(5):632-7.

249. MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. Brain 2000 Apr;123(Pt 4):665-76.

250. MacDonald DB, Purdy RA. Some management problems in adult epilepsy: a review. N S Med Bull 1986;65(4):123-6.

251. Practice parameter: a guideline for discontinuing antiepileptic drugs in seizure-free patients--summary statement. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 1996 Aug;47(2):600-2.

252. Overweg J. Withdrawal of antiepileptic drugs (AEDs) in seizure-free patients, risk factors for relapse with special attention for the EEG. Seizure 1995 Mar;4(1):19-36.

253. Ranganathan LN, Ramaratnam S. Rapid versus slow withdrawal of antiepileptic drugs. Cochrane Database Syst Rev 2006;(2):CD005003.

254. Ranheim B, Dietrichson P, Williamsen R. Prognosis in epilepsy. II. Further report of an investigation. Acta Neurol Scand Suppl 1965;13 Pt 2:497-507.

255. Sackellares JC, Shiau DS, Principe JC, Yang MCK, Dance LK, Suharitdamrong W, Chaovalitwongse W, Pardalos PM, Iasemidis LD. Predictability analysis for an automated seizure prediction algorithm. J Clin Neurophysiol 2006;23(6):509-20.

256. Schmidt D, Loscher W. Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. Acta Neurol Scand 2005 May;111(5):291-300.

257. Sillanpaa M, Shinnar S. Obtaining a driver's license and seizure relapse in patients with childhood-onset epilepsy. Neurology 2005 Feb 22;64(4):680-6.

258. Specchio LM, Beghi E. Should antiepileptic drugs be withdrawn in seizure-free patients? CNS Drugs 2004;18(4):201-12.

259. Specchio LM, Beghi E. Should antiepileptic drugs be withdrawn in seizure-free patients. CNS Drugs 2004;18(4):201-12.

260. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. Epilepsia 2001 Apr;42(4):515-24.

261. Uesugi H, Kojima T, Miyasaka M, Matsuura M, Ohtaka T, Moriiwa M, Shimazono Y. Discontinuation of antiepileptic drug treatment in controlled seizure patients. Jpn J Psychiatry Neurol 1994 Jun;48(2):255-8.

262. Verrotti A, Trotta D, Salladini C, Morgese G, Chiarelli F. Risk factors for recurrence of epilepsy and withdrawal of antiepileptic therapy: a practical approach. Ann Med 2003;35(3):207-15.

263. Wingerchuk DM, Sirven JI. Remission, intractability, and antiepileptic-drug withdrawal. Lancet Neurol 2005;4(7):390-1.

264. Assaf BA, Ebersole JS. Visual and quantitative ictal EEG predictors of outcome after temporal lobectomy. Epilepsia 1999 Jan;40(1):52-61.

265. Berkovic SF, McIntosh AM, Kalnins RM, Jackson GD, Fabinyi GC, Brazenor GA, Bladin PF, Hopper JL. Preoperative MRI predicts outcome of temporal lobectomy: an actuarial analysis. Neurology 1995 Jul;45(7):1358-63.

266. Blume WT, Girvin JP. Altered seizure patterns after temporal lobectomy. Epilepsia 1997 Nov;38(11):1183-7.

267. Brekelmans GJ, Velis DN, van Veelen CW, van Rijen PC, da Silva FH, van Emde Boas W. Intracranial EEG seizure-offset termination patterns: relation to outcome of epilepsy surgery in temporal lobe epilepsy. Epilepsia 1998 Mar;39(3):259-66.

268. Chung CK, Lee SK, Kim KJ. Surgical outcome of epilepsy caused by cortical dysplasia. Epilepsia 2005;46 Suppl 1:25-9.

269. Clusmann H, Schramm J, Kral T, Helmstaedter C, Ostertun B, Fimmers R, Haun D, Elger CE. Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. J Neurosurg 2002 Nov;97(5):1131-41.

270. Ficker DM, So EL, Mosewich RK, Radhakrishnan K, Cascino GD, Sharbrough FW. Improvement and deterioration of seizure control during the postsurgical course of epilepsy surgery patients. Epilepsia 1999 Jan;40(1):62-7.

271. Manno EM, Sperling MR, Ding X, Jaggi J, Alavi A, O'Connor MJ, Reivich M. Predictors of outcome after anterior temporal lobectomy: positron emission tomography. Neurology 1994 Dec;44(12):2331-6.

272. McIntosh AM, Kalnins RM, Mitchell LA, Berkovic SF. Early seizures after temporal lobectomy predict subsequent seizure recurrence. Ann Neurol 2005 Feb;57(2):283-8.

273. Newberg AB, Alavi A, Berlin J, Mozley PD, O'Connor M, Sperling M. Ipsilateral and contralateral thalamic hypometabolism as a predictor of outcome after temporal lobectomy for seizures. J Nucl Med 2000 Dec;41(12):1964-8.

274. Radhakrishnan K, So EL, Silbert PL, Cascino GD, Marsh WR, Cha RH, O'Brien PC. Prognostic implications of seizure recurrence in the first year after anterior temporal lobectomy. Epilepsia 2003 Jan;44(1):77-80.

275. Sirven JI, Malamut BL, Liporace JD, O'Connor MJ, Sperling MR. Outcome after temporal lobectomy in bilateral temporal lobe epilepsy. Ann Neurol 1997 Dec;42(6):873-8.

276. Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, Shinnar S, Langfitt JT, Walczak TS, Pacia SV, Ebrahimi N, Frobish D, Multicenter Study of Epilepsy Surgery. Initial outcomes in the Multicenter Study of Epilepsy Surgery. Neurology 2003 Dec 23;61(12):1680-5.

277. Srikijvilaikul T, Najm IM, Hovinga CA, Prayson RA, Gonzalez-Martinez J, Bingaman WE. Seizure outcome after temporal lobectomy in temporal lobe cortical dysplasia. Epilepsia 2003 Nov;44(11):1420-4.

278. Sylaja PN, Radhakrishnan K, Kesavadas C, Sarma PS. Seizure outcome after anterior temporal lobectomy and its predictors in patients with apparent temporal lobe epilepsy and normal MRI. Epilepsia 2004 Jul;45(7):803-8.

279. Annegers JF, Shirts SB, Hauser WA, Kurland LT. Risk of recurrence after an initial unprovoked seizure. Epilepsia 1986 Jan-Feb;27(1):43-50.

280. Beghi E. A randomized clinical trial of the efficacy and safety of the treatment of the first unprovoked epileptic seizure. First Seizure Trial Group. Neuroepidemiology 1992;11(1):50.

281. Bora I, Seckin B, Zarifoglu M, Turan F, Sadikoglu S, Ogul E. Risk of recurrence after first unprovoked tonic-clonic seizure in adults. J Neurol 1995 Feb;242(3):157-63.

282. National Institute for Health and Clinical Excellence (NICE). Laparoscopic surgery for colorectal cancer (review): costing template and costing report. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Aug. 15 p. (Technology appraisal guidance; no. 105).

283. Chadwick D. Epilepsy after first seizures: risks and implications. J Neurol Neurosurg Psychiatry 1991 May;54(5):385-7.

284. Cleland PG, Mosquera I, Steward WP, Foster JB. Prognosis of isolated seizures in adult life. BMJ 1981;283(6303):1364.

285. Das CP, Sawhney IM, Lal V, Prabhakar S. Risk of recurrence of seizures following single unprovoked idiopathic seizure. Neurol India 2000 Dec;48(4):357-60.

286. Dasheiff R. First seizure management--reconsidered. Response III. Arch Neurol 1987 Nov;44(11):1190-1.

287. van Donselaar CA, Schimsheimer RJ, Geerts AT, Declerck AC. Value of the electroencephalogram in adult patients with untreated idiopathic first seizures. Arch Neurol 1992 Mar;49(3):231-7.

288. Elwes RD, Chesterman P, Reynolds EH. Prognosis after a first untreated tonic-clonic seizure. Lancet 1985 Oct 5;2(8458):752-3.

289. First Seizure Trial Group (FIR.S.T. Group). Randomized clinical trial on the efficacy of antiepileptic drugs in reducing the risk of relapse after a first unprovoked tonic-clonic seizure. Neurology 1993 Mar;43(3 Pt 1):478-83.

290. Fisher RS. First seizure management--reconsidered. Response II. Arch Neurol 1987 Nov;44(11):1189-90.

291. Gupta SK, Satishchandra P, Venkatesh A, Subbakrishna DK. Prognosis of single unprovoked seizure. J Assoc Physicians India 1993 Nov;41(11):709-10.

292. Hart YM, Sander JW, Johnson AL, Shorvon SD. National General Practice Study of Epilepsy: recurrence after a first seizure. Lancet 1990 Nov 24;336(8726):1271-4.

293. Hart RG, Easton JD. Seizure recurrence after a first, unprovoked seizure. Arch Neurol 1986 Dec;43(12):1289-90.

294. Hauser WA, Rich SS, Lee JR, Annegers JF, Anderson VE. Risk of recurrent seizures after two unprovoked seizures. N Engl J Med 1998 Feb 12;338(7):429-34.

295. Hauser WA. Should people be treated after a first seizure. Arch Neurol 1986 Dec;43(12):1287-8.

296. Hauser WA, Anderson VE, Loewenson RB, McRoberts SM. Seizure recurrence after a first unprovoked seizure. N Engl J Med 1982 Aug 26;307(9):522-8.

297. Hui AC, Tang A, Wong KS, Mok V, Kay R. Recurrence after a first untreated seizure in the Hong Kong Chinese population. Epilepsia 2001 Jan;42(1):94-7.

298. Hyllested K, Pakkenberg H. Prognosis in epilepsy of late onset. Neurology 1963 Aug;13:641-4.

299. Kawkabani A, Rossetti AO, Despland PA. Survey of management of first-ever seizures in a hospital based community. Swiss Med Wkly 2004 Oct 2;134(39-40):586-92.

300. Kho LK, Lawn ND, Dunne JW, Linto J. First seizure presentation: do multiple seizures within 24 hours predict recurrence. Neurology 2006 Sep 26;67(6):1047-9.

301. Kim LG, Johnson TL, Marson AG, Chadwick DW, MRC MESS Study group. Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the MESS trial. Lancet Neurol 2006 Apr;5(4):317-22.

302. King MA, Newton MR, Jackson GD, Fitt GJ, Mitchell LA, Silvapulle MJ, Berkovic SF. Epileptology of the first-seizure presentation: a clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. Lancet 1998 Sep 26;352(9133):1007-11.

303. Leone MA, Solari A, Beghi E, FIRST Group. Treatment of the first tonic-clonic seizure does not affect long-term remission of epilepsy. Neurology 2006 Dec 26;67(12):2227-9.

304. Lindsten H, Stenlund H, Forsgren L. Remission of seizures in a population-based adult cohort with a newly diagnosed unprovoked epileptic seizure. Epilepsia 2001 Aug;42(8):1025-30.

305. Lindsten H, Stenlund H, Forsgren L. Seizure recurrence in adults after a newly diagnosed unprovoked epileptic seizure. Acta Neurol Scand 2001 Oct;104(4):202-7.

306. Marson A, Jacoby A, Johnson A, Kim L, Gamble C, Chadwick D, Medical Research Council MESS Study Group. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Lancet 2005 Jun 11-17;365(9476):2007-13.

307. Martinovic Z, Jovic N. Seizure recurrence after a first generalized tonic-clonic seizure, in children, adolescents and young adults. Seizure 1997 Dec;6(6):461-5.

308. Musicco M, Beghi E, Solari A, Viani F. Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy. First Seizure Trial Group (FIRST Group). Neurology 1997 Oct;49(4):991-8.

309. Saunders M, Marshall C. Isolated seizures: an EEG and clinical assessment. Epilepsia 1975 Dec;16(5):731-3.

310. Thomas MH. The single seizures: its study and management. JAMA 1959 Jan 31;169(5):457-9.

311. Abduljabbar M, Ogunniyi A, Daif AK, Al-Tahan A, Al-Bunyan M, Al-Rajeh S. Epilepsy classification and factors associated with control in Saudi adult patients. Seizure 1998 Dec;7(6):501-4.

312. Adamolekun B, Mielke JK, Ball DE. An evaluation of the impact of health worker and patient education on the care and compliance of patients with epilepsy in Zimbabwe. Epilepsia 1999 Apr;40(4):507-11.

313. Aldenkamp AP, Alpherts WC, Moerland MC, Ottevanger N, Van Parys JA. Controlled release carbamazepine: cognitive side effects in patients with epilepsy. Epilepsia 1987 Sep-Oct;28(5):507-14.

314. Aldenkamp AP, Overweg J, Smakman J, Beun AM, Diepman L, Edelbroek P, Gutter T, Mulder OG, vt Slot B, Vledder B. Effect of sabeluzole (R 58,735) on memory functions in patients with epilepsy. Neuropsychobiology 1995;32(1):37-44.

315. Barrett J, Gassman C, Lim P, Hughson C, Zimmerman T. Topiramate (R

316. Beenen LF, Lindeboom J, Trenite DG, Heimans JJ, Snoek FJ, Touw DJ, Ader HJ, Van Alphen HA. Comparative double blind clinical trial of phenytoin and sodium valproate as anticonvulsant prophylaxis after craniotomy: efficacy, tolerability, and cognitive effects. J Neurol Neurosurg Psychiatry 1999;67(4):474-80.

317. Begley CE, Beghi E. The economic cost of epilepsy: a review of the literature. Epilepsia 2002;43 Suppl 4:3-9.

318. Beran RG, Hall L, Michelazzi J. An accurate assessment of the prevalence ratio of epilepsy adequately adjusted by influencing factors. Neuroepidemiology 1985;4(2):71-81.

319. Bill PA, Vigonius U, Pohlmann H, Guerreiro CA, Kochen S, Saffer D, Moore A. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. Epilepsy Res 1997 Jun;27(3):195-204.

320. Bittencourt PR, Mader MJ, Bigarella MM, Doro MP, Gorz AM, Marcourakis TM, Ferreira ZS. Cognitive functions, epileptic syndromes and antiepileptic drugs. Arq Neuropsiquiatr 1992 Mar;50(1):24-30.

321. Boon P, Chauvel P, Pohlmann-Eden B, Otoul C, Wroe S. Dose-response effect of levetiracetam 1000 and 2000 mg/day in partial epilepsy. Epilepsy Res 2002 Jan;48(1-2):77-89.

322. Bootsma HP, Aldenkamp AP, Diepman L, Hulsman J, Lambrechts D, Leenen L, Majoie M, Schellekens A, de Krom M. The effect of antiepileptic drugs on cognition: patient perceived cognitive problems of topiramate versus levetiracetam in clinical practice. Epilepsia 2006 Nov;47 Suppl 2:24-7.

323. Brodie MJ, UK Lamotrigine/Carbamazepine Monotherapy Trial Group, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. Lancet 1995 Feb 25;345(8948):476-9.

324. Brodie MJ, The UK Lamotrigine Elderly Study Group, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. Epilepsy Res 1999 Oct;37(1):81-7.

325. Buck D, Jacoby A, Baker GA, Chadwick DW. Factors influencing compliance with antiepileptic drug regimes. Seizure 1997 Apr;6(2):87-93.

326. Burton LA, Harden C. Effect of topiramate on attention. Epilepsy Res 1997 Apr;27(1):29-32.

327. Cochrane HC, Marson AG, Baker GA, Chadwick DW. Neuropsychological outcomes in randomized controlled trials of antiepileptic drugs: a systematic review of methodology and reporting standards. Epilepsia 1998 Oct;39(10):1088-97.

328. Couldridge L, Kendall S, March A. A systematic overview--a decade of research. The information and counselling needs of people with epilepsy. Seizure 2001 Dec;10(8):605-14.

329. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between clinic visits. Arch Intern Med 1990 Jul;150(7):1509-10.

330. Cramer JA, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. Epilepsy Behav 2002;3(4):338-42.

331. Dawkins JL, Crawford PM, Stammers TG. Epilepsy: a general practice study of knowledge and attitudes among sufferers and non-sufferers. Br J Gen Pract 1993 Nov;43(376):453-7.

332. Dodrill CB, Arnett JL, Hayes AG, Garofalo EA, Greeley CA, Greiner MJ, Pierce MW. Cognitive abilities and adjustment with gabapentin: results of a multisite study. Epilepsy Res 1999 Jun;35(2):109-21.

333. Dodrill CB, Arnett JL, Sommerville KW, Shu V. Cognitive and quality of life effects of differing dosages of tiagabine in epilepsy. Neurology 1997 Apr;48(4):1025-31.

334. Dorland's illustrated medical dictionary. 25th ed. Philadelphia (PA): W.B. Saunders Company; 1974.

335. Doughty J, Baker GA, Jacoby A, Lavaud V. Compliance and satisfaction with switching from an immediate-release to sustained-release formulation of valproate in people with epilepsy. Epilepsy Behav 2003 Dec;4(6):710-6.

336. Dowse R, Futter WT. Outpatient compliance with theophylline and phenytoin therapy. S Afr Med J 1991 Dec 7;80(11-12):550-3.

337. Driessen O, Hoppener R. Plasma levels of phenobarbital and phenytoin in epileptic outpatients. Eur Neurol 1977;15(3):135-42.

338. Drislane FW. Persistent worsening of epilepsy associated with pregnancy. J Epilepsy 1994;7(4):268-72.

339. Dutta S, Reed RC. Effect of delayed and/or missed enteric-coated divalproex doses on valproic acid concentrations: Simulation and dose replacement recommendations for the clinician. J Clin Pharm Ther 2006;31(4):321-9.

340. Edwards VE. Social problems confronting a person with epilepsy in modern society. Proc Aust Assoc Neurol 1974;11:239-43.

341. Eisler J, Mattson RH. Compliance in anticonvulsant drug therapy [abstract]. Epilepsia 1975;16:203.

342. Faught E, Matsuo FU, Schachter S, Messenheimer J, Womble GP. Long-term tolerability of lamotrigine: data from a 6-year continuation study. Epilepsy Behav 2004;5(1):31-6.

343. Feldman RG, Pippenger CE. The relation of anticonvulsant drug levels to complete seizure control. J Clin Pharmacol 1976 Jan;16(1):51-9.

344. Fisher RS, Vickrey BG, Gibson P, Hermann B, Penovich P, Scherer A, Walker S. The impact of epilepsy from the patient's perspective I. Descriptions and subjective perceptions. Epilepsy Res 2000 Aug;41(1):39-51.

345. Freeman S. The realities of clonazepam discontinuation. Psychiatr Serv 1997 Jul;48(7):881-2.

346. Gambardella A, Reutens DC, Andermann F, Cendes F, Gloor P, Dubeau F, Olivier A. Late-onset drop attacks in temporal lobe epilepsy: a reevaluation of the concept of temporal lobe syncope. Neurology 1994;44(6):1074-8.

347. Gillham RA, Blacklaw J, McKee PJ, Brodie MJ. Effect of vigabatrin on sedation and cognitive function in patients with refractory epilepsy. J Neurol Neurosurg Psychiatry 1993 Dec;56(12):1271-5.

348. Gillham R, Kane K, Bryant-Comstock L, Brodie MJ. A double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy with health-related quality of life as an outcome measure. Seizure 2000 Sep;9(6):375-9.

349. Gilliam F, Vazquez B, Sackellares JC, Chang GY, Messenheimer J, Nyberg J, Risner ME, Rudd GD. An active-control trial of lamotrigine monotherapy for partial seizures. Neurology 1998 Oct;51(4):1018-25.

350. GlaxoSmithKline. An open randomised comparison of lamotrigine with valproate as monotherapy in patients with idiopathic generalised epilepsy. Critchley Park: Glaxo Wellcome UK; 2000.

351. Gomes Mda M, Maia Filho Hde S. Medication-taking behavior and drug self regulation in people with epilepsy. Arq Neuropsiquiatr 1998 Dec;56(4):714-9.

352. Gomes Md, Maia Filho Hd, Noe RA. Anti-epileptic drug intake adherence. The value of the blood drug level measurement and the clinical approach. Arq Neuropsiquiatr 1998 Dec;56(4):708-13.

353. Graves NM, Holmes GB, Leppik IE. Compliant populations: variability in serum concentrations. Epilepsy Res Suppl 1988;1:91-9.

354. Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. Interventions for enhancing medication adherence (Review). In: The Cochrane Database of Systematic Reviews [internet]. Issue 4. Hoboken (NJ): John Wiley & Sons, Ltd.; 2005 [accessed 2007 Feb 1]. [Art. No.: CD000011]. Available: DOI: 10.1002/14651858.CD000011.pub2.

355. Helgeson DC, Mittan R, Tan SY, Chayasirisobhon S. Sepulveda Epilepsy Education: the efficacy of a psychoeducational treatment program in treating medical and psychosocial aspects of epilepsy. Epilepsia 1990 Jan-Feb;31(1):75-82.

356. Irving P, Al Dahma A, Srinivasan A, Greenwood R. An audit of admissions of patients with epilepsy to a district general hospital. Seizure 1999 May;8(3):166-9.

357. Jones RM, Butler JA, Thomas VA, Peveler RC, Prevett M. Adherence to treatment in patients with epilepsy: associations with seizure control and illness beliefs. Seizure 2006;15(7):504-8.

358. Juni P, Holenstein F, Sterne J, Bartlett C, Egger M. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. Int J Epidemiol 2002 Feb;31(1):115-23.

359. Kalviainen R, Aikia M, Mervaala E, Saukkonen AM, Pitkanen A, Riekkinen PJ. Long-term cognitive and EEG effects of tiagabine in drug-resistant partial epilepsy. Epilepsy Res 1996 Nov;25(3):291-7.

360. Kobau R, DiIorio C. Epilepsy self-management: a comparison of self-efficacy and outcome expectancy for medication adherence and lifestyle behaviors among people with epilepsy. Epilepsy Behav 2003 Jun;4(3):217-25.

361. Koskiniemi M, Van Vleymen B, Hakamies L, Lamusuo S, Taalas J. Piracetam relieves symptoms in progressive myoclonus epilepsy: a multicentre, randomised, double blind, crossover study comparing the efficacy and safety of three dosages of oral piracetam with placebo. J Neurol Neurosurg Psychiatry 1998 Mar;64(3):344-8.

362. Krumholz A, Grufferman S, Orr ST, Stern BJ. Seizures and seizure care in an emergency department. Epilepsia 1989 Mar-Apr;30(2):175-81.

363. Leach JP, Girvan J, Paul A, Brodie MJ. Gabapentin and cognition: a double blind, dose ranging, placebo controlled study in refractory epilepsy. J Neurol Neurosurg Psychiatry 1997 Apr;62(4):372-6.

364. Lhatoo SD, Wong IC, Polizzi G, Sander JW. Long-term retention rates of lamotrigine, gabapentin, and topiramate in chronic epilepsy. Epilepsia 2000 Dec;41(12):1592-6.

365. Lings S. Increased frequency of driving accidents in epilepsy. Ugeskr Laeger 2002 Apr 1;164(14):1920-2.

366. Lisk DR. Epilepsy pattern and clinic compliance in Sierra Leonean Epileptics. Afr J Neurol Sci 1992;11(1):4-8.

367. Loiseau P, Yuen AW, Duche B, Menager T, Arne-Bes MC. A randomised double-blind placebo-controlled crossover add-on trial of lamotrigine in patients with treatment-resistant partial seizures. Epilepsy Res 1990 Nov;7(2):136-45.

368. Luhdorf K, Jensen LK, Plesner AM. Epilepsy in the elderly: prognosis. Acta Neurol Scand 1986 Nov;74(5):409-15.

369. Macphee GJ, McPhail EM, Butler E, Brodie MJ. Controlled evaluation of a supplementary dose of carbamazepine on psychomotor function in epileptic patients. Eur J Clin Pharmacol 1986;31(2):195-9.

370. Mani KS, Rangan G, Srinivas HV, Srindharan VS, Subbakrishna DK. Epilepsy control with phenobarbital or phenytoin in rural south India: the Yelandur study. Lancet 2001 Apr 28;357(9265):1316-20.

371. Manni R, Ratti MT, Perucca E, Galimberti CA, Tartara A. A multiparametric investigation of daytime sleepiness and psychomotor functions in epileptic patients treated with phenobarbital and sodium valproate: a comparative controlled study. Electroencephalogr Clin Neurophysiol 1993 May;86(5):322-8.

372. Maton S. A blinded parallel group comparison of neurontin (gabapentin) and sodium valproate as add-on therapy in the treatment of partial seizures (protocol 945-430003, NE003). Eastleigh: Parke Davis Medical Division; 1998.

373. Mattson RH, Cramer JA, Collins JF. Aspects of compliance: taking drugs and keeping clinic appointments. Epilepsy Res Suppl 1988;1:111-7.

374. McKee PJ, Blacklaw J, Friel E, Thompson GG, Gillham RA, Brodie MJ. Adjuvant vigabatrin in refractory epilepsy: a ceiling to effective dosage in individual patients? Epilepsia 1993 Sep-Oct;34(5):937-43.

375. McKee PJ, Blacklaw J, Forrest G, Gillham RA, Walker SM, Connelly D, Brodie MJ. A double-blind, placebo-controlled interaction study between oxcarbazepine and carbamazepine, sodium valproate and phenytoin in epileptic patients. Br J Clin Pharmacol 1994 Jan;37(1):27-32.

376. Moher D, Pham, Klassen TP, Schulz KF, Berlin JA, Jadad AR, Liberati A. What contributions do languages other than english make on the results of meta-analyses? J Clin Epidemiol 2000 Sep;53(9):964-72.

377. Nichols ME, Meador KJ, Loring DW. Neuropsychological effects of antiepileptic drugs: a current perspective. Clin Neuropharmacol 1993 Dec;16(6):471-84.

378. Nieto-Barrera M, Brozmanova M, Capovilla G, Christe W, Pedersen B, Kane K, O'Neill F, Lamictal vs. Carbamazepine Study Group. A comparison of monotherapy with lamotrigine or carbamazepine in patients with newly diagnosed partial epilepsy. Epilepsy Res 2001 Aug;46(2):145-55.

379. Nousiainen I, Kalviainen R, Mantyjarvi M. Contrast and glare sensitivity in epilepsy patients treated with vigabatrin or carbamazepine monotherapy compared with healthy volunteers. Br J Ophthalmol 2000;84(6):622-5.

380. Ogbuokiri JE, Aguwa CN. Therapeutic plasma levels of phenytoin: variation in relation to seizure control. Adv Ther 1992;9(2):87-90.

381. Ogunniyi A, Oluwole OS, Osuntokun BO. Two-year remission in Nigerian epileptics. East Afr Med J 1998 Jul;75(7):392-5.

382. Otani K. Risk factors for the increased seizure frequency during pregnancy and puerperium. Folia Psychiatr Neurol Jpn 1985;39(1):33-41.

383. Prevey ML, The Department of Veterans Affairs Epilepsy Cooperative Study 264 Group, Delaney RC, Cramer JA, Cattanach L, Collins JF, Mattson RH. Effect of valproate on cognitive functioning. Comparison with carbamazepine. Arch Neurol 1996 Oct;53(10):1008-16.

384. Pulliainen V, Jokelainen M. Effects of phenytoin and carbamazepine on cognitive functions in newly diagnosed epileptic patients. Acta Neurol Scand 1994 Feb;89(2):81-6.

385. Read CL, Stephen LJ, Stolarek IH, Paul A, Sills GJ, Brodie MJ. Cognitive effects of anticonvulsant monotherapy in elderly patients: a placebo-controlled study. Seizure 1998 Apr;7(2):159-62.

386. Reunanen M, Dam M, Yuen AW. A randomised open multicentre comparative trial of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy. Epilepsy Res 1996 Mar;23(2):149-55.

387. Rimmer EM, Richens A. Adouble blind study of a new drug, gamma-vinyl GABA, in patients with refractory epilepsy. In: Porter RJ, editors. Advances in epileptology: proceedins of XVth epilepsy international symposium. New York: Raven Press; 1984. p. 181-5.

388. Ridsdale L, Robins D, Cryer C, Williams H. Feasibility and effects of nurse run clinics for patients with epilepsy in general practice: randomised controlled trial. Epilepsy Care Evaluation Group. BMJ 1997 Jan 11;314(7074):120-2.

389. Rodin E, Khabbazeh Z, Twitty G, Schmaltz S. The cognitive evoked potential in epilepsy patients. Clin Electroencephalogr 1989 Jul;20(3):176-82.

390. Roman DD, Beniak TE, Nugent S. Memory performance on the intracarotid amobarbital procedure as a predicator of seizure focus. Epilepsy Res 1996 Nov;25(3):243-8.

391. Runge U, Haufe A, Kessler C. Predictors of the course of idiopathic generalized epilepsy with grand mal seizures. J Epilepsy 1996;9(3):170-5.

392. Sachdeo RC. Safety and efficacy of 1200mg/d of oxcarbazepine monotherapy versus placebo in patients with recent-onset partial seizures. Camberley: Novartis Pharmaceuticals UK; 1998.

393. Sander JW, Patsalos PN, Oxley JR, Hamilton MJ, Yuen WC. A randomised double-blind placebo-controlled add-on trial of lamotrigine in patients with severe epilepsy. Epilepsy Res 1990 Aug;6(3):221-6.

394. Saletu B, Grunberger J. Early clinical pharmacological trials with a new anti-epileptic, milacemide, using pharmaco-EEG and psychometry. Methods Find Exp Clin Pharmacol 1984 Jun;6(6):317-30.

395. Schachter SC, Leppik IE, Matsuo F, Messenheimer JA, Faught E, Moore EL, Risner ME. Lamotrigine: A six-month, placebo-controlled, safety and tolerance study. J Epilepsy 1995;8(3):201-9.

396. Schmidt D, Gram L, Brodie M, Kramer G, Perucca E, Kalviainen R, Elger CE. Tiagabine in the treatment of epilepsy--a clinical review with a guide for the prescribing physician. Epilepsy Res 2000 Oct;41(3):245-51.

397. Schmidt D, Canger R, Avanzini G, Battino D, Cusi C, Beck-Mannagetta G, Koch S, Rating D, Janz D. Change of seizure frequency in pregnant epileptic women. J Neurol Neurosurg Psychiatry 1983 Aug;46(8):751-5.

398. Schmidt D. A randomised double-blind placebo controlled crossover add-on trial of lamotrigine in patients with treatment resistant partial seizures (Munich). Report no. H34-18. Beckenham: Wellcome Foundation; 1993.

399. Scott DF. Too many fits. Br J Hosp Med 1984 Dec;32(6):306, 309-11.

400. Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2003 Apr. 49 p. (SIGN publication; no. 70). Also available: http://www.sign.ac.uk/guidelines/fulltext/70/index.html.

401. Semah F, Gimenez F, Longer E, Laplane D, Thuillier A, Baulac M. Carbamazepine and its epoxide: an open study of efficacy and side effects after carbamazepine dose increment in refractory partial epilepsy. Ther Drug Monit 1994 Dec;16(6):537-40.

402. Smith D, Baker G, Davies G, Dewey M, Chadwick DW. Outcomes of add-on treatment with lamotrigine in partial epilepsy. Epilepsia 1993 Mar-Apr;34(2):312-22.

403. Snow DG, Jackson SHD, Skinner D, Mainwaring Burton R, Williams AH. Do patients presenting to accident and emergency departments have low serum anticonvulsant concentrations? Arch Emerg Med 1991;8(1):41-4.

404. Stanaway L, Lambie DG, Johnson RH. Non-compliance with anticonvulsant therapy as a cause of seizures. N Z Med J 1985 Mar 13;98(774):150-2.

405. Steiner TJ, Dellaportas CI, Findley LJ, Gross M, Gibberd FB, Perkin GD, Park DM, Abbott R. Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin. Epilepsia 1999 May;40(5):601-7.

406. Stores G, Williams PL, Styles E, Zaiwalla Z. Psychological effects of sodium valproate and carbamazepine in epilepsy. Arch Dis Child 1992 Nov;67(11):1330-7.

407. Sundqvist A, Nilsson BY, Tomson T. Valproate monotherapy in juvenile myoclonic epilepsy: dose-related effects on electroencephalographic and other neurophysiologic tests. Ther Drug Monit 1999 Feb;21(1):91-6.

408. Sveinbjornsdottir S, Sander JW, Patsalos PN, Upton D, Thompson PJ, Duncan JS. Neuropsychological effects of tiagabine, a potential new antiepileptic drug. Seizure 1994 Mar;3(1):29-35.

409. Takaki S, Kurokawa T, Aoyama T. Monitoring drug noncompliance in epileptic patients: assessing phenobarbital plasma levels. Ther Drug Monit 1985;7(1):87-91.

410. Tan SY, Bruni J. Cognitive-behavior therapy with adult patients with epilepsy: a controlled outcome study. Epilepsia 1986 May-Jun;27(3):225-33.

411. Tan JH, Wilder-Smith E, Lim EC, Ong BK. Frequency of provocative factors in epileptic patients admitted for seizures: a prospective study in Singapore. Seizure 2005 Oct;14(7):464-9.

412. Tanganelli P, Regesta G. Vigabatrin vs. carbamazepine monotherapy in newly diagnosed focal epilepsy: a randomized response conditional cross-over study. Epilepsy Res 1996 Nov;25(3):257-62.

413. Tassinari CA, Michelucci R, Ambrosetto G, Salvi F. Double-blind study of vigabatrin in the treatment of drug-resistant epilepsy. Arch Neurol 1987 Sep;44(9):907-10.

414. Thijs RD, Kerr MP. The outcome of prescribing novel anticonvulsants in an outpatient setting: factors affecting response to medication. Seizure 1998 Oct;7(5):379-83.

415. Thorbecke R. Patients with epilepsy who discontinue treatment. Epilepsy Res Suppl 1988;1:119-24.

416. Tiamkao S, Sawanyawisuth K, Paowana W, Saengsuwan J, Arunpongpaisal S, Chaiyakum A, Phuttharak W, Aaauevitchayapat N, Vannaprasaht S, Tiamkao S, Phunikhom K, Jitpimolmard S. Seizure presenting to the emergency department, Srinagarind Hospital. J Med Assoc Thai 2006 Mar;89(3):362-7.

417. Trostle J. Doctors' orders and patients' self-interest: two views of medication usage. Epilepsy Res Suppl 1988;1:57-69.

418. Troupin A, Ojemann LM, Halpern L, Dodrill C, Wilkus R, Friel P, Feigl P. Carbamazepine--a double-blind comparison with phenytoin. Neurology 1977 Jun;27(6):511-9.

419. Wakamoto H, Nagao H, Hayashi M, Morimoto T. Long-term medical, educational, and social prognoses of childhood-onset epilepsy: a population-based study in a rural district of Japan. Brain Dev 2000 Jun;22(4):246-55.

420. Wang WZ, Wu JZ, Ma GY, Dai XY, Yang B, Wang TP, Yuan CL, Hong Z, Bell GS, Prilipko L, de Boer HM, Sander JW. Efficacy assessment of phenobarbital in epilepsy: a large community-based intervention trial in rural China. Lancet Neurol 2006 Jan;5(1):46-52.

421. Global campaign against epilepsy: out of the shadows. [internet]. World Health Organization (WHO); 1997- [accessed 2007 Jan 25]. [various]. Available: http://www.who.int/mental_health/management/globalepilepsycampaign/en/index.html.

422. Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, Mason A, Golder S, O'Meara S, Sculpher M, Drummond M, Forbes C. Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation. Health Technol Assess 2005 Apr;9(15):1-157, iii-iv.

423. Medicines for epilepsy: side effects. [internet]. Landover (MD): Epilepsy Foundation; 2005 [accessed 2006 Jun 16]. [2 p]. Available: http://www.epilespyfoundation.org.

424. Epilepsy syndromes and related conditions. [internet]. International League Against Epilepsy; [accessed 2007 Jan 24]. [various]. Available: http://www.ilae-epilepsy.org/Visitors/Centre/ctf/syndromes.cfm.

425. Satishchandra P, Gururaj G, Mohammed QD, Senanayake N, Silpakit O. Global campaign against epilepsy: out of the shadows. From Prejudice to hope. World Health Organization (WHO) Regional Office for South East Asia; 2001. What is epilepsy? What is not epilepsy? p. 10-3. Also available: http://www.searo.who.int/LinkFiles/Health_and_Behaviour_W

426. Disability law: inability to drive to work not a disability, court rules. LEGAL EAGLE EYE NEWSL NURS PROF 2001 Sep;9(9):2.

427. Braun E, Christ R. Review of impairment and accident risk for alcohol, drugs and medicines (Prepared under contract no GMA1/2000/27043). [IMMORTAL deliverable R4.1]. Vienna: Austrian Road Safety Board; 2002 Sep 16. 119 p. Also available: http://www.immortal.or.at.

428. Charlton J, Koppel S, O'Hare M, Andrea D, Smith G, Khodr B, Langford J, Odell M, Fildes B. Influence of chronic illness on crash involvement of motor vehicle drivers [Report No. 213]. Victoria, Australia: Monash University Accident Research Centre; 2004 Apr 1. Epilepsy and seizure disorders. p. 193-205. Also available: http://www.monash.edu.au/muarc/reports/muarc213.pdf.

429. Commercial insight: anticonvulsants. How to avoid a brand identity crisis by choosing your battlegrounds carefully. [internet]. DataMonitor; 2004 Sep [accessed 2006 Jun 16]. [4 p]. Available: http://www.piribo.com/publications/therapeutic/cns_neurology/anticonvulsants.html.

430. American Epilepsy Society. Epilepsy surgery. Hartford (CT): American Epilepsy Society; 2004 Sep 1. 18 p. Also available: http://www.aesnet.org/visitors/professionaldevelopment/meded/newppt/surgery/surgerycore.pdf.

431. Ramaekers JG, Kuypers KP, Wood CM, Hockey GR, Jamson S, Birch E. Experimental studies on the effects of licit and illicit drugs on driving performance, psychomotor skills and cognitive function (Prepared under contract no. GM

432. Medical literature review. In: U.S. Department of Transportation, Federal Railroad Administration. Medical standards for railroad workers. Final report. Springfield (VA): National Technical Information Service (NTIS); 2005 Jan. p. 107-12.Also available: http://www.fra.dot.gov/downloads/safety/hazmatch6.pdf.

433. Medical standards programs of U.S. DOT modal administrations. In: U.S. Department of Transportation, Federal Railroad Administration. Medical standards for railroad workers. Final report. Springfield (VA): National Technical Information Service (NTIS); 2005 Jan. p. 15-41.Also available: http://www.fra.dot.gov/downloads/safety/hazmatch2.pdf.

434. Medical standards programs of U.S. railroads. In: U.S. Department of Transportation, Federal Railroad Administration. Medical standards for railroad workers. Final report. Springfield (VA): National Technical Information Service (NTIS); 2005 Jan. p. 69-96.Also available: http://www.fra.dot.gov/downloads/safety/hazmatch4.pdf.

435. Review of accident data. In: U.S. Department of Transportation, Federal Railroad Administration. Medical standards for railroad workers. Final report. Springfield (VA): National Technical Information Service (NTIS); 2005 Jan. p. 97-105.Also available: http://www.fra.dot.gov/downloads/safety/hazmatch5.pdf.

436. Traffic Safety Digest [internet]. National Highway Traffic Safety Administration; [accessed 2006 Sep 1]. North Carolina: Commercial Motor Vehicle (CMV) crash evaluation. [2 p]. Available: http://www.nhtsa.dot.gov/people/outreach/safedige/spring99/sp9919.htm.

437. Aikia M, Jutila L, Salmenpera T, Mervaala E, Kalviainen R. Long-term effects of tiagabine monotherapy on cognition and mood in adult patients with chronic partial epilepsy. Epilepsy Behav 2006 Jun;8(4):750-5.

438. Aikia M, Kalviainen R, Sivenius J, Halonen T, Riekkinen PJ. Cognitive effects of oxcarbazepine and phenytoin monotherapy in newly diagnosed epilepsy: one year follow-up. Epilepsy Res 1992 May;11(3):199-203.

439. Akaho R. The effects of antiepileptic drugs on cognition in normal volunteers. Psychiatry Clin Neurosci 1996 Apr;50(2):61-9.

440. Aldenkamp AP. Cognitive and behavioural assessment in clinical trials: when should they be done? Epilepsy Res 2001 May;45(1-3):155-7; discussion 159-61.

441. Aldenkamp AP, Alpherts WC, Diepman L, van 't Slot B, Overweg J, Vermeulen J. Cognitive side-effects of phenytoin compared with carbamazepine in patients with localization-related epilepsy. Epilepsy Res 1994 Sep;19(1):37-43.

442. Aldenkamp AP, Baker G, Mulder OG, Chadwick D, Cooper P, Doelman J, Duncan R, Gassmann-Mayer C, de Haan GJ, Hughson C, Hulsman J, Overweg J, Pledger G, Rentmeester TW, Riaz H, Wroe S. A multicenter, randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add-on therapy to carbamazepine in patients with partial-onset seizures. Epilepsia 2000 Sep;41(9):1167-78.

443. Aldenkamp AP, Baker GA. The Neurotoxicity Scale--II. Results of a patient-based scale assessing neurotoxicity in patients with epilepsy. Epilepsy Res 1997 Jun;27(3):165-73.

444. Aldenkamp AP, De Krom M, Reijs R. Newer antiepileptic drugs and cognitive issues. Epilepsia 2003;44 Suppl 4:21-9.

445. Aldenkamp AP, Rentmeester T, Hulsman J, Majoie M, Doelman J, Diepman L, Schellekens A, Franken M, Olling M. Pharmacokinetics and cognitive effects of carbamazepine formulations with different dissolution rates. Eur J Clin Pharmacol 1998 Apr;54(2):185-92.

446. Aldenkamp AP, Vermeulen J. Phenytoin and carbamazepine: differential effects on cognitive function. Seizure 1995 Jun;4(2):95-104.

447. Allen JE. Drivers not telling doctors of seizures: some report concealing episodes because they don't want to lose their licenses, a survey finds. L A Times 2003 Apr 7;(Health):F3.

448. Andermann F, Remillard GM, Zifkin BG, Trottier AG, Drouin P. Epilepsy and driving. Can J Neurol Sci 1988 Nov;15(4):371-7.

449. Andrewes DG, Bullen JG, Tomlinson L, Elwes RD, Reynolds EH. A comparative study of the cognitive effects of phenytoin and carbamazepine in new referrals with epilepsy. Epilepsia 1986 Mar-Apr;27(2):128-34.

450. Andrewes DG, Schweitzer I, Marshall N. The comparative cognitive side-effects of lithium, carbamazepine and combined lithium-carbamazepine in patients treated for affective disorders. Hum Psychopharmacol 1990;5(1):41-5.

451. Andrewes DG, Tomlinson L, Elwes RD, Reynolds EH. The influence of carbamazepine and phenytoin on memory and other aspects of cognitive function in new referrals with epilepsy. Acta Neurol Scand Suppl 1984;99:23-30.

452. Armon C, Shin C, Miller P, Carwile S, Brown E, Edinger JD, Paul RG. Reversible parkinsonism and cognitive impairment with chronic valproate use. Neurology 1996;47(3):626-35.

453. Ashton H. Drugs and driving. Adverse Drug React Bull 1983;(98):360-3.

454. Baker GA, Marson AG. Cognitive and behavioural assessments in clinical trials: what type of measure. Epilepsy Res 2001 May;45(1-3):163-7; discussion 169-70.

455. Banks GK, Beran RG. Neuropsychological assessment in lamotrigine treated epileptic patients. Clin Exp Neurol 1991;28:230-7.

456. Baron R. [Pregabalin--clinical evidence and experiences. Krankenpfl J 2005;43(7-10):204-5.

457. Bautista RE, Wludyka P. Driving prevalence and factors associated with driving among patients with epilepsy. Epilepsy Behav 2006;9(4):625-31.

458. Beghi E, Cornaggia CM, Hauser WA, Loeber JN, Thorbecke R, Sonnen AE, Severi S, Zolo P, Specchio LM, Specchio N, Boati E, Defanti CA, Pinto P, Breviario E, Pasolini MP, Antonini L, Aguglia U, Russo C, Gambardella A, et al. Social aspects of epilepsy in the adult in seven European countries. Epilepsia 2000;41(8):998-1004.

459. Begley CE, Annegers JF, Lairson DR, Reynolds TF. Estimating the cost of epilepsy. Epilepsia 1999;40 Suppl 8:8-13.

460. Bell BD. W

461. Bell C, Vanderlinden H, Hiersemenzel R, Otoul C, Nutt D, Wilson S. The effects of levetiracetam on objective and subjective sleep parameters in healthy volunteers and patients with partial epilepsy. J Sleep Res 2002 Sep;11(3):255-63.

462. Bell EC, Willson MC, Wilman AH, Dave S, Silverstone PH. Differential effects of chronic lithium and valproate on brain activation in healthy volunteers. Hum Psychopharmacol 2005;20(6):415-24.

463. Ben-Menachem E. Toward a more pragmatic view of driving and epilepsy. Epilepsy Curr 2004 Jul-Aug;4(4):133-4.

464. Benbadis SR, Blustein JN, Sunstad L. Should patients with psychogenic nonepileptic seizures be allowed to drive. Epilepsia 2000 Jul;41(7):895-7.

465. Beran RG. Epilepsy: an exercise in needs analysis (1981 F H Faulding Memorial Award winning essay). Aust Fam Physician 1982 Apr;11(4):321-2, 324-5.

466. Beran RG. Professional privilege, driving and epilepsy, the doctor's responsibility. Epilepsy Res 1997 Mar;26(3):415-21.

467. Beran RG. The doctor/patient relationship, confidentiality and public responsibility. Med Law 2002;21(3):617-37.

468. Beran RG. Analysis and overview of the guidelines for assessing fitness to drive for commercial and private vehicle drivers. Intern Med J 2005 Jun;35(6):364-8.

469. Berent S, Sackellares JC, Giordani B, Wagner JG, Donofrio PD, Abou-Khalil B. Zonisamide (

470. Berg AT, Engel J Jr. Restricted driving for people with epilepsy. Neurology 1999 Apr 22;52(7):1306-7.

471. Berg AT, Engel J Jr. Hippocampal atrophy and the prognosis of epilepsy: some answers, more questions. Neurology 2006 Jul 11;67(1):12-3.

472. Berg AT, Vickrey BG, Sperling MR, Langfitt JT, Bazil CW, Shinnar S, Walczak TS, Pacia S, Spencer SS. Driving in adults with refractory localization-related epilepsy. Multi-Center Study of Epilepsy Surgery. Neurology 2000 Feb 8;54(3):625-30.

473. Berkovic SF. Epilepsy syndromes: effects on cognition, performance and driving ability. Med Law 2000;19(4):757-61.

474. Berkovic SF. Epilepsy syndromes: effects on cognition, performance and driving ability. Med Law 2001;20(4):547-51.

475. Besag FM. Behavioural effects of the new anticonvulsants. Drug Saf 2001;24(7):513-36.

476. Besag FM. Cognitive and behavioral outcomes of epileptic syndromes: implications for education and clinical practice. Epilepsia 2006 Nov;47 Suppl 2:119-25.

477. Bhatt H, Matharu MS, Henderson K, Greenwood R. An audit of first seizures presenting to an Accident and Emergency department. Seizure 2005 Jan;14(1):58-61.

478. Bielen I, Durrigl V, Hajnsek S, Krmpotic P, Sepic-Grahovac D. Inefficiency of the unselective type of legislation for the assessment of fitness to drive in individuals with epilepsy. Neurol Croat 1999;48(2-3)

479. Binnie CD. Cognitive impairment during epileptiform discharges: is it ever justifiable to treat the EEG? Lancet Neurol 2003 Dec 1;2(12):725-30.

480. Binnie CD, Channon S, Marston D. Learning disabilities in epilepsy: Neurophysiological aspects. Epilepsia 1990;31(4 Suppl):S2-S8.

481. Bittencourt PR, Antoniuk SA, Bigarella MM, da Costa JC, Doro MP, Ferreira AS, Fonseca LC, Gorz AM, Goncalves e Silva GE, Marcourakis T, Tedros GM. Carbamazepine and phenytoin in epilepsies refractory to barbiturates: efficacy, toxicity and mental function. Epilepsy Res 1993 Oct;16(2):147-55.

482. Black AB. Confidentiality and driver licensing authorities. Med Law 2003;22(2):333-43.

483. Black AB, Lai NY. Epilepsy and driving in South Australia--an assessment of compulsory notification. Med Law 1997;16(2):253-67.

484. Block A, Fisher RS. Can patients perform volitional motor acts at the start of a seizure? J Clin Neurophysiol 1999;16(2):141-5.

485. Blum D, Meador K, Biton V, Fakhoury T, Shneker B, Chung S, Mills K, Hammer A, Isojarvi J. Cognitive effects of lamotrigine compared with topiramate in patients with epilepsy. Neurology 2006 Aug 8;67(3):400-6.

486. Blume WT, Luders HO, Mizrahi E, Tassinari C, van Emde Boas W, Engel Jr J. Glossay of descriptive terminology for ictal seimiology. [internet]. International League Against Epilepsy; [accessed 2007 Jan 29]. [14 p]. Available: http://www.ilae-epilepsy.org/Visitors/Centre/ctf/glossary.cfm.

487. Boggs JG. Seizures in medically complex patients. Epilepsia 1997;38 Suppl 4:S55-9.

488. Bonanni E, Galli R, Gori S, Pasquali L, Maestri M, Iudice A, Murri L. Neurophysiological evaluation of vigilance in epileptic patients on monotherapy with lamotrigine. Clin Neurophysiol 2001 Jun;112(6):1018-22.

489. Bonanni E, Galli R, Maestri M, Pizzanelli C, Fabbrini M, Manca ML, Iudice A, Murri L. Daytime sleepiness in epilepsy patients receiving topiramate monotherapy. Epilepsia 2004 Apr;45(4):333-7.

490. Bonanni E, Massetani R, Galli R, Gneri C, Petri M, Iudice A, Murri L. A quantitative study of daytime sleepiness induced by carbamazepine and add-on vigabatrin in epileptic patients. Acta Neurol Scand 1997 Apr;95(4):193-6.

491. Boyle J, Meadows R, Degia A, Hindmarch I. Impairment of driving ability: the assessment of the pharmacodynamics of psychoactive compounds. Neuropsychiatrie 2004;18(3-4):86-99.

492. Bremner JD, Mletzko T, Welter S, Quinn S, Williams C, Brummer M, Siddiq S, Reed L, Heim CM, Nemeroff CB. Effects of phenytoin on memory, cognition and brain structure in post-traumatic stress disorder: a pilot study. J Psychopharmacol 2005;19(2):159-65.

493. Broughton RJ, Guberman A, Roberts J. Comparison of the psychosocial effects of epilepsy and narcolepsy/cataplexy: a controlled study. Epilepsia 1984 Aug;25(4):423-33.

494. Brown S, Bird J. Continuing professional development: medico-legal aspects of epilepsy. Seizure 2002 Apr;11 Suppl A:68-74; quiz 73-4.

495. Browne TR, Mattson RH, Penry JK, Smith DB, Treiman DM, Wilder BJ, Ben-Menachem E, Miketta RM, Sherry KM, Szabo GK. A multicentre study of vigabatrin for drug-resistant epilepsy. Br J Clin Pharmacol 1989;27 Suppl 1:95S-100S.

496. Brunbech L, Sabers A. Effect of antiepileptic drugs on cognitive function in individuals with epilepsy: a comparative review of newer versus older agents. Drugs 2002;62(4):593-604.

497. Bruni J. Antiepileptic drug selection and adverse effects: an overview. Can J Neurol Sci 1994 Aug;21(3):S3-6.

498. Caicoya AG, Serratosa JM. Post-ictal behaviour in temporal lobe epilepsy. Epileptic Disord 2006;8(3):228-31.

499. Cary PL, Johnson CA, Foltz RL, Pape BE. Driving under the influence of phenobarbital. J Forensic Sci 1983;28(2):502-4.

500. Cereghino JJ, Fulghum JE Jr. Survey of existing services and facilities for the epileptic in the state of Mississippi. South Med J 1972 Apr;65(4):401-7.

501. Chadwick D. Driving after and during neurological disorders. Practitioner 1994 Dec;238(1545):830-3.

502. Chadwick DW. Driving restrictions and people with epilepsy. Neurology 2001 Nov 27;57(10):1749-50.

503. Chassiakos LR. Doctor files. Honesty goes by the wayside: with driving privileges at stake, some patients keep mum about failing health. L A Times 2003 JUN 23;(Health):F3.

504. Chaudhry HR, Najam N, De Mahieu C, Raza A, Ahmad N. Clinical use of piracetam in epileptic patients. Curr Ther Res Clin Exp 1992;52(3):355-60.

505. Cheuk DK, Wong V. Acupuncture for epilepsy (Review). In: The Cochrane Database of Systematic Reviews [internet]. Issue 2. Hoboken (NJ): John Wiley & Sons, Ltd.; 2006 [accessed 2009 Sep 29]. [Art. No.: CD005062]. Available: DOI: 10.1002/14651858.CD005062.pub2.

506. Chopra SC, Gupta C, Agarwal AK. Effects of CNS active drugs on manual and computerised psychomotor tests and memory. Asia Pacific J Pharmacol 1993;8(4):219-22.

507. Cicolin A, Magliola U, Giordano A, Terreni A, Bucca C, Mutani R. Effects of levetiracetam on nocturnal sleep and daytime vigilance in healthy volunteers. Epilepsia 2006;47(1):82-5.

508. Cohen AF, Ashby L, Crowley D, Land G, Peck AW, Miller AA. Lamotrigine (BW430C), a potential anticonvulsant. Effects on the central nervous system in comparison with phenytoin and diazepam. Br J Clin Pharmacol 1985 Dec;20(6):619-29.

509. Cornaggia CM, Beghi M, Provenzi M, Beghi E. Correlation between Cognition and Behavior in Epilepsy. Epilepsia 2006 Nov;47 Suppl 2:34-9.

510. Cosbey SH. Drugs and the impaired driver in Northern Ireland: an analytical survey. Forensic Sci Int 1986 Dec;32(4):245-58.

511. Craig I, Tallis R. Impact of valproate and phenytoin on cognitive function in elderly patients: Results of a single-blind randomized comparative study. Epilepsia 1994;35(2):381-90.

512. Cramer JA, De Rue K, Devinsky O, Edrich P, Trimble MR. A systematic review of the behavioral effects of levetiracetam in adults with epilepsy, cognitive disorders, or an anxiety disorder during clinical trials. Epilepsy Behav 2003 Apr;4(2):124-32.

513. Crouch DJ, Peat MA, Chinn DM, Finkle BS. Drugs and driving: a systematic analytical approach. J Forensic Sci 1983 Oct;28(4):945-56.

514. Curran HV, Java R. Memory and psychomotor effects of oxcarbazepine in healthy human volunteers. Eur J Clin Pharmacol 1993;44(6):529-33.

515. Daban C, Martinez-Aran A, Torrent C, Sanchez-Moreno J, Goikolea JM, Benabarre A, Comes M, Colom F, Vieta E. Cognitive functioning in bipolar patients receiving lamotrigine: preliminary results. J Clin Psychopharmacol 2006;26(2):178-81.

516. Dalby MA. Behavioral effects of carbamazepine. Adv Neurol 1975;11:331-44.

517. Dalrymple J, Appleby J. Cross sectional study of reporting of epileptic seizures to general practitioners. BMJ 2000 Jan 8;320(7227):94-7.

518. Dasgupta AK, Saunders M, Dick DJ. Epilepsy in the British Steel Corporation: an evaluation of sickness, accident, and work records. Br J Ind Med 1982 May;39(2):145-8.

519. de Gier JJ. Driving tests with patients. Br J Clin Pharmacol 1984;18 Suppl 1:103S-108S.

520. Deckers CL, Hekster YA, Keyser A, Lammers MW, Meinardi H, Renier WO. Adverse effects in epilepsy therapy. Wait and see or go for it? Acta Neurol Scand 1997 Apr;95(4):248-52.

521. Delcker A, Wilhelm H, Timmann D, Diener HC. Side effects from increased doses of carbamazepine on neuropsychological and posturographic parameters of humans. Eur Neuropsychopharmacol 1997 Aug;7(3):213-8.

522. Devinsky O. Cognitive and behavioral effects of antiepileptic drugs. Epilepsia 1995;36 Suppl 2:S46-65.

523. Dilorio C, Osborne Shafer P, Letz R, Henry T, Schomer DL, Yeager K. The association of stigma with self-management and perceptions of health care among adults with epilepsy. Epilepsy Behav 2003;4(3):259-67.

524. Dijkstra JB, McGuire AM, Trimble MR. The effect of vigabatrin on cognitive function and mood. Hum Psychopharmacol 1992;7(5):319-23.

525. Dodrill CB, Arnett JL, Shu V, Pixton GC, Lenz GT, Sommerville KW. Effects of tiagabine monotherapy on abilities, adjustment, and mood. Epilepsia 1998 Jan;39(1):33-42.

526. Dodrill CB, Temkin NR. Motor speed is a contaminating factor in evaluating the 'cognitive' effects of phenytoin. Epilepsia 1989 Jul-Aug;30(4):453-7.

527. Dodrill CB, Troupin AS. Psychotropic effects of carbamazepine in epilepsy: a double-blind comparison with phenytoin. Neurology 1977 Nov;27(11):1023-8.

528. Dodrill CB, Wilensky AJ. Neuropsychological abilities before and after 5 years of stable antiepileptic drug therapy. Epilepsia 1992 Mar-Apr;33(2):327-34.

529. Donchin O, Sawaki L, Madupu G, Cohen LG, Shadmehr R. Mechanisms influencing acquisition and recall of motor memories. J Neurophysiol 2002 Oct;88(4):2114-23.

530. Drane DL, Meador KJ. Epilepsy, anticonvulsant drugs and cognition. Baillieres Clin Neurol 1996 Dec;5(4):877-85.

531. Drane DL, Williamson DJ, Stroup ES, Holmes MD, Jung M, Koerner E, Chaytor N, Wilensky AJ, Miller JW. Cognitive impairment is not equal in patients with epileptic and psychogenic nonepileptic seizures. Epilepsia 2006;47(11):1879-86.

532. Drazkowski JF. Management of the social consequences of seizures. Mayo Clin Proc 2003 May;78(5):641-9.

533. Duncan JS, Shorvon SD, Trimble MR. Effects of removal of phenytoin, carbamazepine, and valproate on cognitive function. Epilepsia 1990 Sep-Oct;31(5):584-91.

534. Eisenschenk S, Gilmore R. Adult-onset seizures: clinical solutions to a challenging patient work-up. Geriatrics 1999 Nov;54(11):18-9, 22-4, 27-8 passim.

535. Evans RW, Gualtieri CT. Carbamazepine: a neuropsychological and psychiatric profile. Clin Neuropharmacol 1985;8(3):221-41.

536. Finucane AK. Legal aspects of epilepsy. Neurol Clin 1999;17(2):235-43.

537. Finucane AK. Epilepsy, driving and the law. Am Fam Physician 1999 Jan 1;59(1):199-200.

538. Fisher R, Blum D. Clobazam, oxcarbazepine, tiagabine, topiramate, and other new antiepileptic drugs. Epilepsia 1995;36 Suppl 2:S105-14.

539. Fisher RS, Krumholz A. Driving and epilepsy. Md Med J 1988 Oct;37(10):795-8.

540. Fisher RS, Parsonage M, Beaussart M, Bladin P, Masland R, Sonnen AE, Remillard G. Epilepsy and driving: an international perspective. Joint Commission on Drivers' Licensing of the International Bureau for Epilepsy and the International League Against Epilepsy. Epilepsia 1994 May-Jun;35(3):675-84.

541. Forney RB. International seminar research on alcohol, drugs and driving. Pharmakopsychiatr Neuropsychopharmakol 1973 Mar;6(2):104-13.

542. Forsgren L, Bucht G, Eriksson S, Bergmark L. Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. Epilepsia 1996 Mar;37(3):224-9.

543. Fortenberry JC, Brown DB, Shevlin LT. Analysis of drug involvement in traffic fatalities in Alabama. Am J Drug Alcohol Abuse 1986;12(3):257-67.

544. Fountain AJ Jr, Lewis JA, Heck AF. Driving with epilepsy: a contemporary perspective. South Med J 1983 Apr;76(4):481-4.

545. Frankenburg FR, Tohen M, Cohen BM, Lipinski JF Jr. Long-term response to carbamazepine: a retrospective study. J Clin Psychopharmacol 1988 Apr;8(2):130-2.

546. French J, Edrich P, Cramer JA. A systematic review of the safety profile of levetiracetam: a new antiepileptic drug. Epilepsy Res 2001 Nov;47(1-2):77-90.

547. Fritz N, Glogau S, Hoffmann J, Rademacher M, Elger CE, Helmstaedter C. Efficacy and cognitive side effects of tiagabine and topiramate in patients with epilepsy. Epilepsy Behav 2005 May;6(3):373-81.

548. Gadoth N, Vainstein G, Yoffe V. Can police car colored flash light induce electroencephalographic discharges and seizures. Clin Electroencephalogr 2002 Jan;33(1):48-50.

549. Gallassi R, Morreale A, Lorusso S, Ferrari M, Procaccianti G, Lugaresi E, Baruzzi A. Cognitive effects of phenytoin during monotherapy and after withdrawal. Acta Neurol Scand 1987 Apr;75(4):258-61.

550. Gallassi R, Morreale A, Lorusso S, Procaccianti G, Lugaresi E, Baruzzi A. Carbamazepine and phenytoin. Comparison of cognitive effects in epileptic patients during monotherapy and withdrawal. Arch Neurol 1988 Aug;45(8):892-4.

551. Garvin JS. Epileptic drivers in Illinois. Ann Neurol 1979 Sep;6(3):279.

552. George CF. Vigilance impairment: assessment by driving simulators. Sleep 2000 Jun 15;23 Suppl 4:S115-8.

553. Gerbo RM. Question: what criteria are disqualifying for a driver undergoing a department of transportation medical evaluation? J Occup Environ Med 2004;46(7):755-6.

554. Gibson P. An epilepsy information network for North Carolina. N C Med J 1983 Sep;44(9):565-9.

555. Gigli GL, Maschio M, Diomedi M, Placidi F, Silvestri G, Marciani MG. Cognitive performances in newly referred patients with temporal lobe epilepsy: comparison with normal subjects in basal condition and after treatment with controlled-release carbamazepine. Int J Neurosci 1996 Nov;88(1-2):97-107.

556. Gigli GL, Placidi F, Diomedi M, Maschio M, Silvestri G, Scalise A, Marciani MG. Nocturnal sleep and daytime somnolence in untreated patients with temporal lobe epilepsy: changes after treatment with controlled-release carbamazepine. Epilepsia 1997 Jun;38(6):696-701.

557. Gillham R, Baker G, Thompson P, Birbeck K, McGuire A, Tomlinson L, Eckersley L, Silveira C, Brown S. Standardisation of a self-report questionnaire for use in evaluating cognitive, affective and behavioural side-effects of anti-epileptic drug treatments. Epilepsy Res 1996 May;24(1):47-55.

558. Gillham R, Bryant-Comstock L, Kane K. Validation of the Side Effect and Life Satisfaction (SEALS) inventory. Seizure 2000 Oct;9(7):458-63.

559. Gillham RA, Read CL, McKee PJ, Larkin JG, Brodie MJ. Cognitive function in adult epileptic patients on long-term sodium valproate. J Epilepsy 1991;4(4):205-10.

560. Gillham RA, Williams N, Wiedmann K, Butler E, Larkin JG, Brodie MJ. Concentration-effect relationships with carbamazepine and its epoxide on psychomotor and cognitive function in epileptic patients. J Neurol Neurosurg Psychiatry 1988 Jul;51(7):929-33.

561. Gillham RA, Williams N, Wiedmann KD, Butler E, Larkin JG, Brodie MJ. Cognitive function in adult epileptic patients established on anticonvulsant monotherapy. Epilepsy Res 1990 Dec;7(3):219-25.

562. Glasgow GL. Epilepsy beginning in adult life. N Z Med J 1979 Nov 28;90(648):433-6.

563. Goldberg JF, Burdick KE. Cognitive side effects of anticonvulsants. J Clin Psychiatry 2001;62 Suppl 1:27-33.

564. Grattan E, Jeffcoate GO. Medical factors and road accidents. Br Med J 1968 Jan 13;1(584):75-9.

565. Grazia Marciani M, Maschio MC, Spanedda F, Gigli GL, Bassetti MA, Bernardi G. Sodium valproate and mental processes in newly referred epileptic patients. A computerized EEG study. Neuropsychobiology 1995;31(4):210-5.

566. Groselj J. Epilepsy and driving license regulations in Slovenia. Med Law 1997;16(2):289-94.

567. Gualtieri CT, Johnson LG. Comparative neurocognitive effects of 5 psychotropic anticonvulsants and lithium. Medscape Gen Med 2006;8(3)

568. Guiden M. Shedding light on epilepsy: advocacy groups are pushing to raise awareness about epilepsy and encourage legislatures to make it a more integral part of public health programs. State Legis 2003 May;29(5):30-31, 33.

569. Hamilton MJ, Cohen AF, Yuen AW, Harkin N, Land G, Weatherley BC, Peck AW. Carbamazepine and lamotrigine in healthy volunteers: Relevance to early tolerance and clinical trial dosage. Epilepsia 1993;34(1):166-73.

570. Harden CL, Lazar LM, Pick LH, Nikolov B, Goldstein MA, Carson D, Ravdin LD, Kocsis JH, Labar DR. A beneficial effect on mood in partial epilepsy patients treated with gabapentin. Epilepsia 1999 Aug;40(8):1129-34.

571. Harding GF, Alford CA, Powell TE. The effect of sodium valproate on sleep, reaction times, and visual evoked potential in normal subjects. Epilepsia 1985 Nov-Dec;26(6):597-601.

572. Harvey P, Hopkins A. Views of British neurologists on epilepsy, driving, and the law. Lancet 1983 Feb 19;1(8321):401-4.

573. Hashimoto K. Sociomedical aspects of temporal lobe epilepsy. Jpn J Psychiatry Neurol 1994 Jun;48(2):205-8.

574. Heaney D. The pharmacoeconomics of the new antiepileptic drugs. Epilepsia 1999;40 Suppl 8:25-31.

575. Helbach D. A legislative view of driving and legal restriction. Wis Med J 1991 Mar;90(3):119-20.

576. Helmstaedter C, Kockelmann E. Cognitive outcomes in patients with chronic temporal lobe epilepsy. Epilepsia 2006 Nov;47 Suppl 2:96-8.

577. Helmstaedter C, Kurthen M. Memory and epilepsy: characteristics, course, and influence of drugs and surgery. Curr Opin Neurol 2001 Apr;14(2):211-6.

578. Helmstaedter C, Wagner G, Elger CE. Differential effects of first antiepileptic drug application on cognition in lesional and non-lesional patients with epilepsy. Seizure 1993 Jun;2(2):125-30.

579. Herner B, Smedby B, Ysander L. Sudden illness as a cause of motor-vehicle accidents. Br J Ind Med 1966 Jan;23(1):37-41.

580. Hindmarch I. The psychopharmacology of clobazam. Hum Psychopharmacol 1995;10(Suppl 1):S15-25.

581. Hindmarch I, Dawson J, Stanley N. A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo. Sleep 2005 FEB 1;28(2):187-93.

582. Hirsch E, Genton P. Antiepileptic drug-induced pharmacodynamic aggravation of seizures: does valproate have a lower potential. CNS Drugs 2003;17(9):633-40.

583. Hirsch E, Schmitz B, Carreno M. Epilepsy, antiepileptic drugs (AEDs) and cognition. Acta Neurol Scand Suppl 2003;180:23-32.

584. Hocking B. Assessing fitness to drive. Aust Fam Physician 2003 Sep;32(9):737.

585. Hockings N, Pall A, Moody J, Davidson AV, Davidson DL. The effects of age on carbamazepine pharmacokinetics and adverse effects. Br J Clin Pharmacol 1986 Dec;22(6):725-8.

586. Holden EW, Thanh Nguyen H, Grossman E, Robinson S, Nelson LS, Gunter MJ, Von Worley A, Thurman DJ. Estimating prevalence, incidence, and disease-related mortality for patients with epilepsy in managed care organizations. Epilepsia 2005 Feb;46(2):311-9.

587. Hopkins A, Scambler G. How doctors deal with epilepsy. Lancet 1977 Jan 22;1(8004):183-6.

588. Hughes JT, Devinsky O. Legal aspects of epilepsy. Neurol Clin 1994 Feb;12(1):203-23.

589. Husain M, Rizvi SJ, Usmani JA, Hanif SA. Epilepsy and the law: an Indian perspective. J Clin Forensic Med 2002;9(2):61-4.

590. Ieiri I, Hirata K, Higuchi S, Kojima K, Ikeda M, Yamada H, Aoyama T. Pharmacoepidemiological study on adverse reactions of antiepileptic drugs. Chem Pharm Bull (Tokyo) 1992;40(5):1280-8.

591. Inoue Y, Ito M, Kurihara M, Morimoto K, Commission on Legal Affairs, Japan Epilepsy Society (Japan chapter of. Epilepsy and driving in Japan. Epilepsia 2004 Dec;45(12):1630-5.

592. Iudice A, Bonanni E, Maestri M, Nucciarone B, Brotini S, Manca L, Iudice G, Murri L. Lormetazepam effects on daytime vigilance, psychomotor performance and simulated driving in young adult healthy volunteers. Int J Clin Pharmacol Ther 2002 Jul;40(7):304-9.

593. Jeavons PM, Harding GF, Panayiotopoulos CP. Photosensitive epilepsy and driving. Lancet 1971 May 29;1(7709):1125.

594. Jeffery WK, Hindmarsh KW, Mullen PW. The involvement of drugs in driving in Canada: an update to 1994. Can Soc Forensic Sci J 1996;29(2):93-8.

595. Jha S, Nag D, Shukla R, Kar AM, Saxena RC, Trivedi JK. Changes in cognitive functions in epileptics on sodium valproate monotherapy. Indian J Physiol Pharmacol 1992 Apr;36(2):135-6.

596. Jokeit H, Kramer G, Ebner A. Do antiepileptic drugs accelerate forgetting. Epilepsy Behav 2005 May;6(3):430-2.

597. Jokeit H, Okujava M, Woermann FG. Carbamazepine reduces memory induced activation of mesial temporal lobe structures: a pharmacological fM

598. Kalviainen R. Cognitive effects of GABAergic antiepileptic drugs. Electroencephalogr Clin Neurophysiol Suppl 1999;50:458-64.

599. Kalviainen R. Long-term safety of tiagabine. Epilepsia 2001;42 Suppl 3:46-8.

600. Kanner AM, Wuu J, Faught E, Tatum WO 4th, Fix A, French JA. A past psychiatric history may be a risk factor for topiramate-related psychiatric and cognitive adverse events. Epilepsy Behav 2003 Oct;4(5):548-52.

601. Kaplan PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: nonconvulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. J Clin Neurophysiol 1999 Jul;16(4):341-52; discussion 353.

602. Kasteleijn-Nolst Trenite DG, Vermeiren R. The impact of subclinical epileptiform discharges on complex tasks and cognition: relevance for aircrew and air traffic controllers. Epilepsy Behav 2005;6(1):31-4.

603. Kendrick AM, Duncan JS, Trimble MR. Effects of discontinuation of individual antiepileptic drugs on mood. Hum Psychopharmacol 1993;8(4):263-270.

604. Kent GP, Schefft BK, Howe SR, Szaflarski JP, Yeh H-S, Privitera MD. The effects of duration of intractable epilepsy on memory function. Epilepsy Behav 2006;9(3):469-77.

605. Ketter TA, Post RM, Theodore WH. Positive and negative psychiatric effects of antiepileptic drugs in patients with seizure disorders. Neurology 1999;53(5 Suppl 2):S53-67.

606. King D, Benbow SJ, Barrett JA. The law and medical fitness to drive--a study of doctors' knowledge. Postgrad Med J 1992 Aug;68(802):624-8.

607. Kingham LA. Driving and epilepsy: changing the law in Maryland. Epilepsia 1994 May-Jun;35(3):693-5.

608. Kipervasser S, Andelman F, Kramer U, Nagar S, Fried I, Neufeld MY. Effects of topiramate on memory performance on the intracarotid amobarbital (Wada) test. Epilepsy Behav 2004;5(2):197-203.

609. Kisacanin B, Agarwal GC, Taber J, Hier D. Computerised evaluation of cognitive and motor function. Med Biol Eng Comput 2000 Jan;38(1):68-73.

610. Kockelmann E, Elger CE, Helmstaedter C. Cognitive profile of topiramate as compared with lamotrigine in epilepsy patients on antiepileptic drug polytherapy: relationships to blood serum levels and comedication. Epilepsy Behav 2004 Oct;5(5):716-21.

611. Koh SH, Kim J, Kim HT, Kim SH, Kim MH, Yu HJ. A survey to investigate the opinions of physicians, who treat epilepsy, about the automobile driving by epilepsy patients in Korea. Neurol Psychiatry brain res 2003;10(4):159-64.

612. Kolpan KI. Can a physician be held liable for certifying a person with a seizure history fit to drive? J Head Trauma Rehabil 1988 Jun;3(2):97.

613. Kotsopoulos IA, Evers SM, Ament AJ, de Krom MC. Estimating the costs of epilepsy: an international comparison of epilepsy cost studies. Epilepsia 2001 May;42(5):634-40.

614. Kozena L, Frantik E, Horvath M. Pharmacologically induced decrease in vigilance measured by two different psychological methods. Homeost Health Dis 1997;38(2):64-5.

615. Krumholz A. Driving and epilepsy: a historical perspective and review of current regulations. Epilepsia 1994 May;35(3):668-74.

616. Kudoh A, Matsuki A. Current perception thresholds of epileptic patients treated with valproate. Seizure 2000;9(7):498-501.

617. Kuhl V, Kiorboe E, Lund M. The prognosis of epilepsy with special reference to traffic security. Epilepsia 1967 Sep;8(3):195-209.

618. Kuitunen T, Mattila MJ, Seppala T, Aranko K, Mattila ME. Actions of zopiclone and carbamazepine, alone and in combination, on human skilled performance in laboratory and clinical tests. Br J Clin Pharmacol 1990 Sep;30(3):453-61.

619. Kuruvilla A, Devi V. Drugs influencing cognitive function. Indian J Physiol Pharmacol 1994 Oct;38(4):241-51.

620. Kwan P, Brodie MJ. Neuropsychological effects of epilepsy and antiepileptic drugs. Lancet 2001 Jan 20;357(9251):216-22.

621. Landau WM. More on epilepsy and epileptic drivers. Ann Neurol 1979 Aug;6(2):140.

622. Langfitt JT. Cost evaluations in epilepsy: an update. Epilepsia 2000;41 Suppl 2:S62-8.

623. Larkin JG, McLellan A, Munday A, Sutherland M, Butler E, Brodie MJ. A double-blind comparison of conventional and controlled-release carbamazepine in healthy subjects. Br J Clin Pharmacol 1989 Mar;27(3):313-22.

624. LeBlang TR. Epilepsy, motor vehicle licensure and the law. IMJ Ill Med J 1979 Jun;155(6):367-73.

625. Lee HW, Jung DK, Suh CK, Kwon SH, Park SP. Cognitive effects of low-dose topiramate monotherapy in epilepsy patients: a 1-year follow-up. Epilepsy Behav 2006;8(4):736-41.

626. Lee S, Sziklas V, Andermann F, Farnham S, Risse G, Gustafson M, Gates J, Penovich P, Al-Asmi A, Dubeau F, Jones-Gotman M. The effects of adjunctive topiramate on cognitive function in patients with epilepsy. Epilepsia 2003 Mar;44(3):339-47.

627. Legros B, Bazil CW. Effects of antiepileptic drugs on sleep architecture: a pilot study. Sleep Med 2003;4(1):51-5.

628. Levy P. Economic evaluation of antiepileptic drug therapy: a methodologic review. Epilepsia 2002 May;43(5):550-8.

629. Lhatoo SD, Sander JW, Wong IC. Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. Neurology 2000 Jan 11;54(1):270-1; author reply 271-2.

630. Lindsten H, Stenlund H, Edlund C, Forsgren L. Socioeconomic prognosis after a newly diagnosed unprovoked epileptic seizure in adults: a population-based case-control study. Epilepsia 2002 Oct;43(10):1239-50.

631. Linnoila M, Mattila MJ. Proceedings: Drug interaction on driving skills as evaluated by laboratory tests and by a driving simulator. Pharmakopsychiatr Neuropsychopharmakol 1973 Mar;6(2):127-32.

632. Loring DW, Hermann BP, Lee GP, Drane DL, Meador KJ. The Memory Assessment Scales and lateralized temporal lobe epilepsy. J Clin Psychol 2000 Apr;56(4):563-70.

633. Lucki I, Rickels K, Geller AM. Chronic use of benzodiazepines and psychomotor and cognitive test performance. Psychopharmacology (Berl) 1986;88(4):426-33.

634. Lutz MT, Helmstaedter C. EpiTrack: tracking cognitive side effects of medication on attention and executive functions in patients with epilepsy. Epilepsy Behav 2005;7(4):708-14.

635. MacPhee GJ, Goldie C, Roulston D, Potter L, Agnew E, Laidlaw J, Brodie MJ. Effect of carbamazepine on psychomotor performance in naive subjects. Eur J Clin Pharmacol 1986;30(1):37-42.

636. Makatsori A, Duncko R, Moncek F, Loder I, Katina S, Jezova D. Modulation of neuroendocrine response and non-verbal behavior during psychosocial stress in healthy vVolunteers by the glutamate release-inhibiting drug lamotrigine. Neuroendocrinology 2004;79(1):34-42.

637. Manni R, Ratti MT, Galimberti CA, Morini R, Perucca E, Tartara A. Daytime sleepiness in epileptic patients on long-term monotherapy: MSLT, clinical and psychometric assessment. Neurophysiol Clin 1993 Jan;23(1):71-6.

638. Marciani MG, Maschio MC, Spanedda F, Gigli GL, Bassetti MA, Bernardi G. Sodium valproate and mental processes in newly referred epileptic patients. A computerized EEG study. Neuropsychobiology 1995;31(4):210-5.

639. Marciani MG, Spanedda F, Mattia D. Neurophysiologic and neuropsychologic profiles of lamotrigine in epilepsy. Clin Neuropharmacol 1999 May-Jun;22(3):159-63.

640. Marciani MG, Stanzione P, Mattia D, Spanedda F, Bassetti MA, Maschio M, Bernardi G. Lamotrigine add-on therapy in focal epilepsy: electroencephalographic and neuropsychological evaluation. Clin Neuropharmacol 1998 Jan-Feb;21(1):41-7.

641. Marciani MG, Stefanini F, Stefani N, Sabbadini M, Gigli GL, Bernardi G. Effect of carbamazepine treatment on EEG changes induced by different cortical activation patterns in newly referred epileptic patients. Neuropsychobiology 1992;25(4):221-6.

642. Marks V. Drugs and driving. R Soc Health J 1982;102(5):205-10.

643. Martin R, Griffith HR, Sawrie S, Knowlton R, Faught E. Determining empirically based self-reported cognitive change: development of reliable change indices and standardized regression-based change norms for the multiple abilities self-report questionnaire in an epilepsy sample. Epilepsy Behav 2006 Feb;8(1):239-45.

644. Martin R, Kuzniecky R, Ho S, Hetherington H, Pan J, Sinclair K, Gilliam F, Faught E. Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. Neurology 1999 Jan 15;52(2):321-7.

645. Martin R, Meador K, Turrentine L, Faught E, Sinclair K, Kuzniecky R, Gilliam F. Comparative cognitive effects of carbamazepine and gabapentin in healthy senior adults. Epilepsia 2001;42(6):764-71.

646. Matsuura M. Patient satisfaction with polypharmacy reduction in chronic epileptics. Psychiatry Clin Neurosci 2000 Apr;54(2):249-53.

647. Mattila MJ, Aranko K, Mattila ME, Paakkari I. Effects of psychotropic drugs on digit substitution: comparison of the computerized symbol-digit substitution and traditional digit-symbol substitution tests. J Psychopharmacol 1994;8(2):81-7.

648. Mattson RH. Cognitive, affective, and behavioral side events in adults secondary to antiepileptic drug use. Rev Neurol Dis 2004;1 Suppl 1:S10-7.

649. McKee PJW, Blacklaw J, Butler E, Gillham RA, Brodie MJ. Variability and clinical relevance of the interaction between sodium valproate and carbamazepine in epileptic patients. Epilepsy Res 1992;11(3):193-8.

650. Meador KJ. Cognitive side effects of antiepileptic drugs. Can J Neurol Sci 1994 Aug;21(3):S12-6.

651. Meador KJ. Cognitive and behavioral assessments in AED trials. Adv Neurol 1998;76:231-8.

652. Moyer DL. Relapse treatment and prevention in an outpatient rehabilitation program. Special Issue: Relapse: Conceptual, research and clinical perspectives. J Chem Depend Treat 1989;2(2):225-40.

653. Meador KJ. Newer anticonvulsants: dosing strategies and cognition in treating patients with mood disorders and epilepsy. J Clin Psychiatry 2003;64(Suppl 8):30-4.

654. Meador KJ. Cognitive and memory effects of the new antiepileptic drugs. Epilepsy Res 2006 Jan;68(1):63-7.

655. Meador KJ, Baker GA. Behavioral and cognitive effects of lamotrigine. J Child Neurol 1997 Nov;12(Suppl 1):S44-7.

656. Meador KJ, Loring DW, Abney OL, Allen ME, Moore EE, Zamrini EY, King DW. Effects of carbamazepine and phenytoin on EEG and memory in healthy adults. Epilepsia 1993 Jan-Feb;34(1):153-7.

657. Meador KJ, Loring DW, Allen ME, Zamrini EY, Moore EE, Abney OL, King DW. Comparative cognitive effects of carbamazepine and phenytoin in healthy adults. Neurology 1991 Oct;41(10):1537-40.

658. Meador KJ, Loring DW, Huh K, Gallagher BB, King DW. Comparative cognitive effects of anticonvulsants. Neurology 1990 Mar;40(3 Pt 1):391-4.

659. Meador KJ, Loring DW, Hulihan JF, Kamin M, Karim R, CAP

660. Meador KJ, Loring DW, Moore EE, Thompson WO, Nichols ME, Oberzan RE, Durkin MW, Gallagher BB, King DW. Comparative cognitive effects of phenobarbital, phenytoin, and valproate in healthy adults. Neurology 1995 Aug;45(8):1494-9.

661. Meador KJ, Loring DW, Ray PG, Murro AM, King DW, Nichols ME, Deer EM, Goff WT. Differential cognitive effects of carbamazepine and gabapentin. Epilepsia 1999 Sep;40(9):1279-85.

662. Meador KJ, Loring DW, Ray PG, Murro AM, King DW, Perrine KR, Vazquez BR, Kiolbasa T. Differential cognitive and behavioral effects of carbamazepine and lamotrigine. Neurology 2001 May 8;56(9):1177-82.

663. Meador KJ, Loring DW, Vahle VJ, Ray PG, Werz MA, Fessler AJ, Ogrocki P, Schoenberg MR, Miller JM, Kustra RP. Cognitive and behavioral effects of lamotrigine and topiramate in healthy volunteers. Neurology 2005 Jun 28;64(12):2108-14.

664. Mecarelli O, Rinalduzzi S, Accornero N. Changes in Color Vision after a Single Dose of Vigabatrin or Carbamazepine in Healthy Volunteers. Clin Neuropharmacol 2001 Jan-Feb;24(1):23-6.

665. Mecarelli O, Vicenzini E, Pulitano P, Vanacore N, Romolo FS, Di Piero V, Lenzi GL, Accornero N. Clinical, cognitive, and neurophysiologic correlates of short-term treatment with carbamazepine, oxcarbazepine, and levetiracetam in healthy volunteers. Ann Pharmacother 2004 Nov;38(11):1816-22.

666. Social aspects of epilepsy in the adult in seven European countries. The RESt-1 Group. Epilepsia 2000 Aug;41(8):998-1004.

667. Centers for Disease Control and Prevention (CDC). Prevalence of epilepsy and health-related quality of life and disability among adults with epilepsy--South Carolina, 2003 and 2004. MMWR Morb Mortal Wkly Rep 2005 Oct 28;54(42):1080-2.

668. Michelucci R, Cavaciocchi P, Riguzzi P, Passarelli D, Parmeggiani L, Santangelo M, Zamagni M, Iudice A, Tassinari CA. Single-blind, placebo-controlled dose-modification study of vigabatrin in refractory epileptic patients. J Epilepsy 1992;5(4):248-52.

669. Miller LL, Pellock JM, Boggs JG, DeLorenzo RJ, Meyer JM, Corey LA. Epilepsy and seizure occurrence in a population-based sample of Virginian twins and their families. Epilepsy Res 1999 Apr;34(2-3):135-43.

670. Moodley P, Golombok S, Lader M. Effects of clorazepate dipotassium and placebo on psychomotor skills. Percept Mot Skills 1985 Dec;61(3 Pt 2):1121-2.

671. Morita Y. [Cognitive impairment of antiepileptic medication. Nippon Rinsho 2004 Jan;62 Suppl:475-8.

672. Mortimore C, Trimble M, Emmers E. Effects of gabapentin on cognition and quality of life in patients with epilepsy. Seizure 1998 Oct;7(5):359-64.

673. Mosher CG, Rozance JE. Neurologists look at driving and lapses of consciousness. Semin Neurol 1987 Dec;7(4):372-6.

674. Moskowitz H. Attention tasks as skills performance measures of drug effects. Br J Clin Pharmacol 1984;18 Suppl 1:51S-61S.

675. Mula M, Trimble MR, Thompson P, Sander JW. Topiramate and word-finding difficulties in patients with epilepsy. Neurology 2003 Apr 8;60(7):1104-7.

676. Murthy JM, Yangala R. Acute symptomatic seizures - incidence and etiological spectrum: a hospital-based study from South India. Seizure 1999 May;8(3):162-5.

677. Nadkarni S, Devinsky O. Psychotropic effects of antiepileptic drugs. Epilepsy Curr 2005 Sep-Oct;5(5):176-81.

678. Neyens LG, Alpherts WC, Aldenkamp AP. Cognitive effects of a new pyrrolidine derivative (levetiracetam) in patients with epilepsy. Prog Neuropsychopharmacol Biol Psychiatry 1995 May;19(3):411-9.

679. Neyens LG, Alpherts WC, Aldenkamp AP, Neyens LG. Cognitive effects of a new pyrrolidine derivative (levetiracetam) in patients with epilepsy. Prog Neuropsychopharmacol Biol Psychiatry 1995;19(3):411-9.

680. Ng HW. Driving and work safety. Practitioner 1991 Feb;235(1499):174-6.

681. O'Brien SJ. The controversy surrounding epilepsy and driving: a review. Public Health 1986 Jan;100(1):21-7.

682. O'Donoghue MF, Duncan JS, Sander JW. The subjective handicap of epilepsy. A new approach to measuring treatment outcome. Brain 1998 Feb;121(Pt 2):317-43.

683. O'Dougherty M, Wright FS, Cox S, Walson P. Carbamazepine plasma concentration. Relationship to cognitive impairment. Arch Neurol 1987 Aug;44(8):863-7.

684. O'Hanlon JF. Discussion of 'Medications and the Safety of the Older Driver' by Ray et al.. Hum Factors 1992;34(1):49-51.

685. Ogunrin O, Adamolekun B, Ogunniyi A. Cognitive effects of anti-epileptic drugs in Nigerians with epilepsy. Afr J Neurol Sci 2005;24(1)

686. Ojemann LM, Ojemann GA, Dodrill CB, Crawford CA, Holmes MD, Dudley DL. Language Disturbances as Side Effects of Topiramate and Zonisamide Therapy. Epilepsy Behav 2001 Dec;2(6):579-584.

687. Ooi WW, Gutrecht JA. International regulations for automobile driving and epilepsy. J Travel Med 2000 Jan;7(1):1-4.

688. Ott BR, Mernoff ST. Driving policy issues and the physician. Med Health R I 1999 Dec;82(12):428-31.

689. Ottman R, Lipton RB. Comorbidity of migraine and epilepsy. Neurology 1994 Nov;44(11):2105-10.

690. Owczarek K, Jedrzejczak J, Rozenek H. Cognitive functioning in neuropsychological tests and self-ratings in patients with epilepsy. Acta Neuropsychol 2006;4(1-2)

691. Ozkara C, Hanoglu L, Keskinkilic C, Yeni N, Aysal F, Uzan M, Ozyurt E, Karaagac N. Memory in patients with drug-responsive mesial temporal lobe epilepsy and hippocampal sclerosis. Epilepsia 2004;45(11):1392-6.

692. Ozuna J. Ethical dilemmas in epilepsy and driving. J Epilepsy 1993;6(3):185-8.

693. Ozuna J. Ethical dilemmas in people with epilepsy who drive. Clin Nurs Pract Epilepsy 1998 Mar;5(1):7-10.

694. Pachlatko C. The relevance of health economics to epilepsy care. Epilepsia 1999;40 Suppl 8:3-7.

695. Pacia SV, Devinsky O. Clozapine-related seizures: experience with 5,629 patients. Neurology 1994 Dec;44(12):2247-9.

696. Palva ES, Linnoila M. Effect of active metabolites of chlordiazepoxide and diazepam, alone or in combination with alcohol, on psychomotor skills related to driving. Eur J Clin Pharmacol 1978 Jul 30;13(5):345-50.

697. Panagopoulos GR, Thomaides T, Tagaris G, Karageorgiou CL. Auditory event related potentials in patients with epilepsy on sodium valproate monotherapy. Acta Neurol Scand 1997;96(1):62-4.

698. Paradowski B, Zagrajek MM. Epilepsy in middle-aged and elderly people: a three-year observation. Epileptic Disord 2005 Jun;7(2):91-5.

699. Parsonage MJ. Epilepsy and driving: some of the problems. Nurs Times 1970 Apr 30;66(18):555-6.

700. Pellock JM. Tricyclic anticonvulsants: safety and adverse effects. Epilepsy Behav 2002;3(3 II):S14-7.

701. Perper JA. Medicolegal implications of epilepsy. Leg Med Annu 1978;:105-24.

702. Piazzini A, Chifari R, Canevini MP, Turner K, Fontana SP, Canger R. Levetiracetam: an improvement of attention and of oral fluency in patients with partial epilepsy. Epilepsy Res 2006;68(3):181-8.

703. Pieters MS, van Steveninck AF, Schoemaker RC, Kroon JM, van Gerven JM, Cohen AF. The psychomotor effects of carbamazepine in epileptic patients and healthy volunteers. J Psychopharmacol (Oxf) 2003 Sep;17(3):269-72.

704. Placidi F, Marciani MG, Diomedi M, Scalise A, Pauri F, Giacomini P, Gigli GL. Effects of lamotrigine on nocturnal sleep, daytime somnolence and cognitive functions in focal epilepsy. Acta Neurol Scand 2000 Aug;102(2):81-6.

705. Febrile seizures. NIH Consens Statement Online. [online]. National Institues of Health; 1980 May 29-21 [accessed 2002 Feb 28]. Available: http://consensus.nih.gov/cons/023/023_statement.htm.

706. Prevey ML, Delaney RC, Cramer JA, Cattanach L, Collins JF, Mattson RH. Effect of valproate on cognitive functioning: comparison with carbamazepine. Arch Neurol 1996;53(10):1008-16.

707. Prevey ML, Delaney RC, Cramer JA, Mattson RH. Complex partial and secondarily generalized seizure patients: cognitive functioning prior to treatment with antiepileptic medication. VA Epilepsy Cooperative Study 264 Group. Epilepsy Res 1998 Mar;30(1):1-9.

708. Prevey ML, Mattson RH, Cramer JA. Improvement in cognitive functioning and mood state after conversion to valproate monotherapy. Neurology 1989 Dec;39(12):1640-1.

709. Pulliainen V, Jokelainen M. Comparing the cognitive effects of phenytoin and carbamazepine in long-term monotherapy: a two-year follow-up. Epilepsia 1995 Dec;36(12):1195-202.

710. Quaglieri CE. Physician responsibility for epileptics' compliance with motor vehicle laws. J Leg Med (N Y) 1977 Jan;5(1):8

711. Rabasseda X. Oxcarbazepine: anticonvulsant profile and safety. Drugs Today 2001;37(5):333-55.

712. Raffle PA. Fitness to drive. Trans Med Soc Lond 1974;90:197-205.

713. Raffle PA. Drugs and driving. Prescr J 1981;21(3):197-204.

714. Rahmann A, Stodieck S, Husstedt I-W, Evers S. Pre-attentive cognitive processing in epilepsy: a pilot study on the impact of epilepsy type and anti-epileptic treatment. Eur Neurol 2002;48(3):146-52.

715. Ramaekers G, Lamers J, Verhey F, Muntjewerff D, Mobbs E, Sanders N, Lewis M, Lockton A. A comparative study of the effects of carbamazepine and the NMDA receptor antagonist remacemide on road tracking and car-following performance in actual traffic. Psychopharmacology (Berl) 2002 Jan;159(2):203-10.

716. Ramaratnam S, Baker GA, Goldstein LH. Psychological treatments for epilepsy (Review). In: The Cochrane Database of Systematic Reviews [internet]. Issue 4. Hoboken (NJ): John Wiley & Sons, Ltd.; 2005 [accessed 2006 Sep 29]. [Art. No.: CD002029]. Available: DOI: 10.1002/14651858.CD002029.pub2.

717. Ramaratnam S, Sridharan K. Yoga for epilepsy (Review). In: The Cochrane Database of Systematic Reviews [internet]. Issue 1. Hoboken (NJ): John Wiley & Sons, Ltd.; 2002 [accessed 2006 Sep 29]. [Art. No. CD001524]. Available: DOI: 10.1002/14651858.CD001524.

718. Ranganathan LN, Ramaratnam S. Vitamins for epilepsy (Review). In: The Cochrane Database of Systematic Reviews [internet]. Issue 2. Hoboken (NJ): John Wiley & Sons, Ltd.; 2005 [accessed 2006 Sep 29]. [Art. No. CD004304]. Available: DOI: 10.1002/14651858.CD004304.pub2.

719. Understanding cervical cancer: a women's guide. Chicao (IL): Gynecologic Cancer Foundation (GCF); 17 p.

720. Rapeport WG, Williams SA, Muirhead DC, Dewland PM, Tanner T, Wesnes K. Absence of a sertraline-mediated effect on the pharmacokinetics and pharmacodynamics of carbamazepine. J Clin Psychiatry 1996;57(Suppl 1):20-3.

721. Ravi Sudhir RV, Sawhney IMS, Prabhakar S, Pershad D, Nain CK. Comparative cognitive effects of phenytoin and carbamazepine in adult epileptics. Neurol India 1995;43(4):186-92.

722. Ray A, Pathak-Ray V, Walters R, Hatfield R. Driving after epilepsy surgery: effects of visual field defects and epilepsy control. Br J Neurosurg 2002 Oct;16(5):456-60.

723. Ray WA, Gurwitz J, Decker MD, Kennedy DL. Medications and the safety of the older driver: is there a basis for concern? Hum Factors 1992;34(1):33-47.

724. Reuben W. Epilepsy, driving and the pharmaceutical industry--legal responsibility. Med Law 2002;21(3):639-50.

725. Reynolds EH, Trimble MR. Adverse neuropsychiatric effects of anticonvulsant drugs. Drugs 1985 Jun;29(6):570-81.

726. Richards KC. Patient page. The risk of fatal car crashes in people with epilepsy. Neurology 2004 Sep 28;63(6):E12-3.

727. Riddle CN, Baker MR, Baker SN. The effect of carbamazepine on human corticomuscular coherence. Neuroimage 2004 May;22(1):333-40.

728. Ridsdale L, Kwan I, Morgan M. How can a nurse intervention help people with newly diagnosed epilepsy? A qualitative study of patients' views. Seizure 2003;12(2):69-73.

729. Risse GL. Cognitive outcomes in patients with frontal lobe epilepsy. Epilepsia 2006 Nov;47 Suppl 2:87-9.

730. Rizzo V, Quartarone A, Bagnato S, Battaglia F, Majorana G, Girlanda P. Modification of cortical excitability induced by gabapentin: a study by transcranial magnetic stimulation. Neurol Sci 2001;22(3):229-32.

731. Rogawski MA, Loscher W. The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. Nat Med 2004 Jul;10(7):685-92.

732. Rosche J, Uhlmann C, Weber R, Froscher W. Different cognitive effects of inducing levetiracetam or topiramate into an antiepileptic pharmacotherapy in patients with therapy refractory epilepsy. Neurol Psychiatry brain res 2004;11(3):109-14.

733. Rostock A, Hoffmann W, Siegemund C, Bartsch R. Effects of carbamazepine, valproate calcium, clonazepam and piracetam on behavioral test methods for evaluation of memory-enhancing drugs. Methods Find Exp Clin Pharmacol 1989;11(9):547-53.

734. Russ W. Vigabatrin in unsatisfactory controlled epilepsies. Schweiz Arch Neurol Psychiatr 1995;146(2):55-9.

735. Ryan J, Nash S, Lyndon J. Epilepsy in the accident and emergency department - developing a code of safe practice for adult patients. J Accid Emerg Med 1998;15(4):237-43.

736. Ryan J, Nash S, Lyndon J. Epilepsy in the accident and emergency department--developing a code of safe practice for adult patients. South East and South West Thames Accident and Emergency Specialty Sub-committees. J Accid Emerg Med 1998 Jul;15(4):237-43.

737. Sabers A, Moller A, Dam M, Smed A, Arlien-Soborg P, Buchman J, Andersen EB, Boesen F, Dam AM, Lyon BB, et al.. Cognitive function and anticonvulsant therapy: effect of monotherapy in epilepsy. Acta Neurol Scand 1995 Jul;92(1):19-27.

738. Saletu B, Grunberger J, Linzmayer L. Evaluation of encephalotropic and psychotropic properties of gabapentin in man by pharmaco-EEG and psychometry. Int J Clin Pharmacol Ther Toxicol 1986 Jul;24(7):362-73.

739. Salinsky MC, Binder LM, Oken BS, Storzbach D, Aron CR, Dodrill CB. Effects of gabapentin and carbamazepine on the EEG and cognition in healthy volunteers. Epilepsia 2002 May;43(5):482-90.

740. Salinsky MC, Oken BS, Binder LM. Assessment of drowsiness in epilepsy patients receiving chronic antiepileptic drug therapy. Epilepsia 1996 Feb;37(2):181-7.

741. Salinsky MC, Spencer DC, Oken BS, Storzbach D. Effects of oxcarbazepine and phenytoin on the EEG and cognition in healthy volunteers. Epilepsy Behav 2004 Dec;5(6):894-902.

742. Salinsky MC, Storzbach D, Spencer DC, Oken BS, Landry T, Dodrill CB. Effects of topiramate and gabapentin on cognitive abilities in healthy volunteers. Neurology 2005 Mar 8;64(5):792-9.

743. Salinsky MC, Wegener K, Sinnema F. Epilepsy, driving laws, and patient disclosure to physicians. Epilepsia 1992 May-Jun;33(3):469-72.

744. Sanzenbacher KE. The 'other' aspects of the epilepsies. J Maine Med Assoc 1977 Feb;68(2):37-8.

745. Sasagawa M, Hasegawa S, Tamura K, Kaneko K, Kaji S. Relationship between a driver's license and employment situation for people with epilepsy. Jpn J Psychiatry Neurol 1989 Sep;43(3):548-9.

746. Schachter SC. Symptoms of a seizure. [internet]. Reston (VA): Epilepsy Therapy Development Project; 2004 Sep 30 [accessed 2006 Nov 3]. [3 p]. Available: http://www.epilepsy.com/101/ep101_symptom.html.

747. Schain RJ, Dreisbach M. Phenobarbital and cognitive function. Pediatrics 1982 Aug;70(2):326-7.

748. Schmedding E, Belgian Working Group on Epilepsy and Driving.. Epilepsy and driving in Belgium: proposals and justification. Acta Neurol Belg 2004 Jun;104(2):68-79.

749. Schmidt RP, Wilder BJ. Epilepsy and the law: a commentary from the United States perspective. In: Pedley TA, Meldrum BS. Recent advances in epilepsy. Vol. 4. New York (NY): Churchill Livingstone, Inc.; 1988. p. 253-7.

750. Seigel AM. Driving and epilepsy. The case for reform in Connecticut. Conn Med 1988 Feb;52(2):70-1.

751. Selwa LM, Berent S, Giordani B, Henry TR, Buchtel HA, Ross DA. Serial cognitive testing in temporal lobe epilepsy: longitudinal changes with medical and surgical therapies. Epilepsia 1994 Jul-Aug;35(4):743-9.

752. Seppala T, Linnoila M, Mattila MJ. Drugs, alcohol and driving. Drugs 1979 May;17(5):389-408.

753. Serafetinides EA. Psychosocial aspects of neurosurgical management of epilepsy. Adv Neurol 1975;8:323-32.

754. Sharp GB. Driving and epilepsy: the state of the matter. J Ark Med Soc 1994 Oct;91(5):222-4.

755. Shinnar S, Hauser WA. Do occasional brief seizures cause detectable clinical consequences. Prog Brain Res 2002;135:221-35.

756. Shorvon S. Epilepsy and driving. BMJ 1995 Apr 8;310(6984):885-6.

757. Sillanpaa M, Schmidt D. Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. Brain 2006 Mar;129(Pt 3):617-24.

758. Smith DB. Cognitive effects of antiepileptic drugs. Adv Neurol 1991;55:197-212.

759. Smith ME, Gevins A, McEvoy LK, Meador KJ, Ray PG, Gilliam F. Distinct cognitive neurophysiologic profiles for lamotrigine and topiramate. Epilepsia 2006 Apr;47(4):695-703.

760. Smith ML. Psychosocial comorbidity in epilepsy. Adv Neurol 2006;97:333-7.

761. Sohn YH, Jung HY, Kaelin-Lang A, Hallett M. Effect of levetiracetam on rapid motor learning in humans. Arch Neurol 2002 Dec;59(12):1909-12.

762. Sperling R, Greve D, Dale A, Killiany R, Holmes J, Rosas HD, Cocchiarella A, Firth P, Rosen B, Lake S, Lange N, Routledge C, Albert M. Functional MRI detection of pharmacologically induced memory impairment. Proc Natl Acad Sci U S A 2002 Jan 8;99(1):455-60.

763. Stapleton JM, Guthrie S, Linnoila M. Effects of alcohol and other psychotropic drugs on eye movements: relevance to traffic safety. J Stud Alcohol 1986 Sep;47(5):426-32.

764. Starr DS. The legal advisor. A clinician's duty to warn: the family of a man killed in a car accident sues the epileptic driver's PA for negligence. Clin Advisor 2003 Aug 25;6(8):85-6.

765. Steinwall O. Epilepsy and driver's licence-some comments. Scand J Rehabil Med 1972;4(3):123-5.

766. Stewart SA. The effects of benzodiazepines on cognition. J Clin Psychiatry 2005;66 Suppl 2:9-13.

767. Stratton WT. Motorists with seizure disorders. Kans Med 1992 Feb;93(2):38.

768. Strauss E, Hunter M, Wada J. Risk factors for cognitive impairment in epilepsy. Neuropsychology 1995 Oct;9(4):457-63.

769. Swann AC. Major system toxicities and side effects of anticonvulsants. J Clin Psychiatry 2001;62 Suppl 1:16-21.

770. Tassinari CA, Rubboli G. Cognition and paroxysmal EEG activities: from a single spike to electrical status epilepticus during sleep. Epilepsia 2006;47(Suppl 2):40-3.

771. Tata PR, Rollings J, Collins M, Pickering A, Jacobson RR. Lack of cognitive recovery following withdrawal from long-term benzodiazepine use. Psychol Med 1994 Feb;24(1):203-13.

772. Taylor JF. Some aspects of the health of long-distance drivers. Proc R Soc Med 1977 Apr;70(4):243-6.

773. Taylor JF. The influence of physical disease and its treatment on driving performance. In: Burley D, Silverstone T. Medicines and road traffic safety. London (UK): CNS (Clinical Neuroscience); 1988. p. 55-7.

774. Thomas L, Trimble M. The effects of vigabatrin on attention, concentration and mood: An investigation in healthy volunteers. Seizure 1996;5(3):205-8.

775. Thomas SV. Money matters in epilepsy. Neurol India 2000 Dec;48(4):322-9.

776. Thompson P, Huppert F, Trimble M. Anticonvulsant drugs, cognitive function and memory. Acta Neurol Scand Suppl 1980;80:75-81.

777. Thompson P, Huppert FA, Trimble M. Phenytoin and cognitive function: effects on normal volunteers and implications for epilepsy. Br J Clin Psychol 1981 Sep;20(Pt 3):155-62.

778. Thompson PJ. Antiepileptic drugs and memory. Epilepsia 1992;33 Suppl 6:S37-40.

779. Thompson PJ, Baxendale SA, Duncan JS, Sander JW. Effects of topiramate on cognitive function. J Neurol Neurosurg Psychiatry 2000 Nov;69(5):636-41.

780. Thompson PJ, Trimble MR. Sodium valproate and cognitive functioning in normal volunteers. Br J Clin Pharmacol 1981 Dec;12(6):819-24.

781. Thompson PJ, Trimble MR. Anticonvulsant drugs and cognitive functions. Epilepsia 1982 Oct;23(5):531-44.

782. Thorbecke R. Epilepsy and driving licence in the Federal Republic of Germany and other European countries. Jpn J Psychiatry Neurol 1991 Jun;45(2):313-7.

783. Trimble M. The effect of anti-convulsant drugs on cognitive abilities. Pharmacol Ther [B] 1979;4(3):677-85.

784. Trimble M. Anticonvulsant drugs, behavior, and cognitive abilities. Curr Dev Psychopharmacol 1981;6:65-91.

785. Trimble MR. Anticonvulsant drugs and cognitive function: a review of the literature. Epilepsia 1987;28 Suppl 3:S37-45.

786. Trimble MR. Cognitive effects of anticonvulsants. Neurology 1991 Aug;41(8):1326.

787. Trimble MR, Thompson PJ. Anticonvulsant drugs, cognitive function, and behavior. Epilepsia 1983;24(Suppl 1):S55-63.

788. Trimble MR, Thompson PJ. Sodium valproate and cognitive function. Epilepsia 1984;25 Suppl 1:S60-4.

789. Trimble R. [Cognitive effects of antiepileptic drugs]. Rev Neurol (Paris) 1987;143(5):420-8.

790. Tuunainen A, Hurskainen H, Nousiainen U, Pilke A, Riekkinen P. Short-term withdrawal of antiepileptic medication: effects on attention and memory. Acta Neurol Scand 1995 Sep;92(3):198-205.

791. Unsworth C. Living with epilepsy: safety during home, leisure and work activities. Aust Occup Ther J 1999;46(3):89-98.

792. Van der Meyden CH, Bartel PR, Sommers DK, Blom M, Becker P, Erasmus S, Griesel D. Effect of acute doses of controlled-release carbamazepine on clinical, psychomotor, electrophysiological, and cognitive parameters of brain function. Epilepsia 1992;33(2):335-42.

793. Van der Meyden CH, Rodda JL. Epilepsy management at primary health care level. S Afr Med J 2000;90(4 II):403-32.

794. Verma NP, Yusko MJ, Greiffenstein MF. Carbamazepine offers no psychotropic advantage over phenytoin in adult epileptic subjects. Seizure 1993 Mar;2(1):53-6.

795. Vining EP. Cognitive dysfunction associated with antiepileptic drug therapy. Epilepsia 1987;28 Suppl 2:S18-22.

796. Voorhies TM. Cognitive and behavioral effects of antiepileptic drugs. Semin Neurol 1988 Spring;8(1):35-41.

797. Walsh DJ. Epilepsy and driving privileges. Kans Med 1987 Mar;88(3):81-3, 97.

798. Werz MA, Schoenberg MR, Meador KJ, Loring DW, Ray PG, Kaul-Gupta R, Ogrocki P. Subjective preference for lamotrigine or topiramate in healthy volunteers: relationship to cognitive and behavioral functioning. Epilepsy Behav 2006 Feb;8(1):181-91.

799. West JC. Failure to comply with state notification statute may be failure to warn. Harden v. Allstate Ins. Co. J Healthc Risk Manag 1996 Spring;16(2):33-5.

800. White JR, Walczak TS, Leppik IE, Rarick J, Tran T, Beniak TE, Matchinsky DJ, Gumnit RJ. Discontinuation of levetiracetam because of behavioral side effects: a case-control study. Neurology 2003 Nov 11;61(9):1218-21.

801. Whyte J, Wroblewski B. Effects of phenytoin on cognitive function. N Engl J Med 1989 Jul 6;321(1):53-4.

802. Wiebe S, Bellhouse DR, Fallahay C, Eliasziw M. Burden of epilepsy: the Ontario Health Survey. Can J Neurol Sci 1999 Nov;26(4):263-70.

803. Wildin JD, Pleuvry BJ, Mawer GE. Impairment of psychomotor function at modest plasma concentrations of carbamazepine after administration of the liquid suspension to naive subjects. Br J Clin Pharmacol 1993 Jan;35(1):14-9.

804. Willette RE, Walsh JM. Drugs, driving, and traffic safety. WHO Offset Publ 1983;(78)

805. Withaar FK, Brouwer WH, van Zomeren AH. Fitness to drive in older drivers with cognitive impairment. J Int Neuropsychol Soc 2000 May;6(4):480-90.

806. Wong IC, Lhatoo SD. Adverse reactions to new anticonvulsant drugs. Drug Saf 2000;23(1):35-56.

807. Zaccara G, Gangemi PF, Messori A, Parigi A, Massi S, Valenza T, Monza GC. Effects of oxcarbazepine and carbamazepine on the central nervous system: computerised analysis of saccadic and smooth-pursuit eye movements. Acta Neurol Scand 1992 Jun;85(6):425-9.

808. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [internet]. Ottawa (ON): Ottawa Health Research Institute (OHRI); [accessed 2006 May 11]. [2 p]. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.

Appendix A: Search Summaries

Search Information Pertaining to Key Question 1- Crash Risk

Electronic Database Searches

The following databases have been searched for relevant information:

Name	Date limits	Platform/provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1990 through January 16, 2007	OVID
Cochrane Library	Through 2007 Issue 1	www.thecochranelibrary.com
Embase (Excerpta Medica)	1990 through January 24, 2007	OVID
Medline	1990 through January 16, 2007	OVID
PubMed (Premedline)	Premedline[sb] Searched January 15, 2007	www.pubmed.gov
TRIS Online (Transportation Research Information Service Database)	Through September 18, 2006	http://trisonline.bts.gov/search.cfm

Hand Searches of Journal and Nonjournal Literature

Journals and supplements maintained in ECRI's collections were routinely reviewed. Nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

Controlled Vocabulary Headings (MeSH, EMTREE, PsycINFO Subject Headings) and Keywords

Conventions:

$ = truncation character (wildcard) in OVID syntax
exp = "explodes" controlled vocabulary term. E.g. expands search to all more specific related terms in the vocabulary's hierarchy.
.de. = limit controlled vocabulary heading in OVID syntax
.fc. = form/content type (PsycINFO – OVID syntax)
.fs. =floating subheading in OVID syntax
.hw. = limit to heading word in OVID syntax
.mp. =combined search fields in OVID syntax (default if no fields are specified)
.pt. =publication Type in OVID syntax
.ti. =limit to title in OVID syntax
.tw. =limit to title and abstract fields in OVID syntax

Topic-specific Search Terms

Accidents

Accidents, traffic

Accident$.ti.
Collision$.ti.
Crash$.ti.
Highway safety
Motor traffic accidents
Traffic safety
Wreck$.ti.

Anticonvulsants
Anticonvulsants
anticonvulsive agent
anticonvulsive drugs
Acetazolamide
Antiepilepsirine
apo-acetazolamide
apo-carbamazepine
Carbamazepine
Celontin
Cerebyx
Depakene
Depakote
Diamox
Dilantin
Ecovia
Epitol
Epival
Ethosuximide
Felbamate
Felbatol
Fosphenytoin
Gabapentin
Imipramine
Keppra
Lamictal
Lamotrigine
Luminal
Mazepine
Mentat
Methsuximide
Neurontin
Novocarbamaz
Oxcarbazepine
Phenobarbital
Phenytoin
Piracetam

Primidone
Remacemide
Sinemet
Tegretol
Tiagabine
TMO
Tofranil
Topiramate
Tridione
Trileptal
Trimethadione
Trimethinum
Troxidone
Valproic acid
Zarontin
Zonegran
Zonisamide

Driving
Automobile driver examination
Automobile driving
Automobiles
Car driving
Driving.ti.
Driving behavior
Motor vehicles

Mental Processes
Aware$
Choice behavior
Cognition
Continuous performance test
Divided attention task
Eye movement
Mental function
Mental processes
Neuropsychological performance
Perceptual motor processes
Performance
Psychomotor
Psychomotor performance
Reaction time
Response latency
Risk taking
Road tracking test

Unaware$

Seizures
Convuls$
Epilepsy
Epilep$
Fits
Seizure$
seizures

Embase/Medline/Cinahl (English language, human)

Set Number	Concept	Search statement
1	Seizures	Exp epilepsy/ or exp seizures/ or (seizure$ or epilep$ or convuls$ or fits).ti.
2	Anticonvulsants	exp anticonvulsants/ or exp anticonvulsive agent/ or exp anticonvulsive drugs/ OR acetazolamide OR apo-acetazolamide OR diamox OR antiepilepsirine OR mentat OR carbamazepine OR tegretol OR apo-carbamazepine OR epitol OR mazepine OR novocarbamaz OR sinemet OR ethosuximide OR zarontin OR felbamate OR felbatol OR fosphenytoin OR cerebyx OR gabapentin OR neurontin OR imipramine OR tofranil OR lamotrigine OR lamictal OR keppra OR methsuximide OR celontin OR oxcarbazepine OR trileptal OR Phenobarbital OR luminal OR phenytoin OR dilantin OR piracetam OR primidone OR remacemide OR ecovia OR tiagabine OR topiramate OR trimethadione OR tridione OR tmo OR trimethinum OR troxidone OR valproic acid OR depakene OR depakote OR epival OR zonisamide OR zonegran
3	Mental processes	Exp mental processes/ or exp psychomotor/ or exp neuropsychological performance or exp performance/ or exp reaction time/ or exp mental function/ or exp response latency/ or exp cognition/ or exp perceptual motor processes/ or exp psychomotor performance/
4	Accidents	Accidents, traffic.de. or highway safety.de. or motor traffic accidents.de. or traffic accident.de. or traffic safety.de. or crash$.ti. or wreck$.ti. or collision.ti. or accident$.ti.
5	Driving	Automobile driving.de. or exp motor vehicles/ or automobiles.de. or exp driving behavior/ or exp car driving/ or exp motor vehicle/ or driving.ti. or (driving or commercial or professional or truck or car or auto$ or long distance or haul$).ti.
6	Attention	Aware or continuous performance test or road tracking test or divided attention task or eye movement or unaware
7	Risk-taking	Risk-taking.de. or choice behavior
8	Combine sets	(1 or 2) and (3 or 4 or 5 or 6)
9	Remove overlap	Remove duplicates from 8
10	Limit by publication type	9 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
11	Limit by study type	10 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebo or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study).de. or random$.hw. or random$.ti. or placebo$ or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham)) or latin square or ISRTCN)

PreMedline (PubMed)

Set Number	Concept	Search statement
1	Seizures	Epilepsy OR "convulsive disorder" OR "convulsive disorders" OR "seizure disorder" OR "seizure disorders" OR seizure*[ti])
2	Driving	automobile driving OR motor vehicles OR accidents, traffic OR automobile driver examination OR driving OR car*[ti] OR automob*[ti] OR vehicle*[ti] OR traffic*[ti] OR driv*[ti] OR licens*[ti] OR (highway AND safety) OR crash* OR collision* OR wreck* OR truck* OR tractor* OR driver*)
3	Cognition	Mental processes OR psychomotor performance OR reaction time OR attention* OR percept* OR "executive function" OR "decision-making" OR "decision making" OR judgment OR planning OR memory OR "motor function" OR neuropsychological OR metacognition OR cognit* OR psychomotor* OR "eye movement" OR "continuous performance" OR risk taking OR choice behavior OR "response latency"
4	Anticonvulsants	acetazolamide OR apo-acetazolamide OR diamox OR antiepilepsirine OR mentat OR carbamazepine OR tegretol OR apo-carbamazepine OR epitol OR mazepine OR novocarbamaz OR sinemet OR ethosuximide OR zarontin OR felbamate OR felbatol OR fosphenytoin OR cerebyx OR gabapentin OR neurontin OR imipramine OR tofranil OR lamotrigine OR lamictal OR keppra OR methsuximide OR celontin OR oxcarbazepine OR trileptal OR Phenobarbital OR luminal OR phenytoin OR dilantin OR piracetam OR primidone OR remacemide OR ecovia OR tiagabine OR topiramate OR trimethadione OR tridione OR tmo OR trimethinum OR troxidone OR valproic acid OR depakene OR depakote OR epival OR zonisamide OR zonegran
5	Combine sets	(#1 OR #4) AND (#2 OR #3)
6	Limit	#5 AND (in process[sb] OR publisher[sb])

Search Strategies for Key Questions 2, 3 and 4 (Seizure Recurrence)

Electronic Database Searches

The following databases have been searched for relevant information:

Name	Date limits	Platform/provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1990 through January 16, 2007	OVID
Cochrane Library	Through 2007 Issue 1	www.thecochranelibrary.com
Embase (Excerpta Medica)	1990 through January 24, 2007	OVID
Medline	1990 through January 16, 2007	OVID
PubMed (Premedline)	Premedline[sb] Searched January 15, 2007	www.pubmed.gov
TRIS Online (Transportation Research Information Service Database)	Through September 18, 2006	http://trisonline.bts.gov/search.cfm

Hand Searches of Journal and Nonjournal Literature

Journals and supplements maintained in ECRI's collections were routinely reviewed. Nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.).

Controlled Vocabulary Headings (MeSH, EMTREE, PsycINFO Subject Headings) and Keywords

Conventions:

$ = truncation character (wildcard) in OVID syntax
exp = "explodes" controlled vocabulary term. E.g. expands search to all more specific related terms in the vocabulary's hierarchy.
.de. = limit controlled vocabulary heading in OVID syntax
.fc. = form/content type (PsycINFO – OVID syntax)
.fs. =floating subheading in OVID syntax
.hw. = limit to heading word in OVID syntax
.mp. =combined search fields in OVID syntax (default if no fields are specified)
.pt. =publication Type in OVID syntax
.ti. =limit to title in OVID syntax
.tw. =limit to title and abstract fields in OVID syntax

Topic-specific Search Terms

Modifying concepts
Discontinu$
Drug withdrawal/
First
Solitary
Unprovoked
Withdrawal

Outcome
Follow-up
Long-term
Longitudinal
Outcome.de.
Treatment outcome

Recurrence
Recur$
Recurrence
Relapse
Relaps$

Risk
Proportional hazard models.de.
Risk/
Risk$

Seizures
Convuls$
Epilepsy

Epilep$
Fits
Seizure$
seizures

Embase/Medline/Cinahl (English language, human)

Set Number	Concept	Search statement
1	Seizures	Exp epilepsy/ or exp seizures/ or (seizure$ or epilep$ or convuls$ or fits).ti.
2	Risk	Exp risk/ or risk$.ti. or proportional hazard models.de. or proportional hazards model.de.
3	Withdrawal of medication	(Withdrawal or discontinue$).ti. or *drug withdrawal/
4	First occurrence	(unprovoked or first or solitary).ti.
5	Recurrence	*recurrence/ or *relapse/ or recurrent disease.de. or *recurrence risk/ or (recur$ or relaps$).ti.
6	Combine sets	1 and 2 and (3 or 4) and 5
7	Remove overlap	Remove duplicates from 6
8	Limit by publication type	7 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
9	Limit by study type	8 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebo or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study).de. or random$.hw. or random$.ti. or placebo$ or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham)) or latin square or ISRTCN)

PreMedline (PubMed)

Set Number	Concept	Search statement
1	Seizures	Epilepsy OR “convulsive disorder” OR “convulsive disorders” OR “seizure disorder” OR “seizure disorders” OR seizure*[ti])
2	Recurrence	Recur* OR relaps*
3	Combine sets	#1 AND #2
4	Limit	#3 AND (in process[sb] OR publisher[sb])

Search Strategies for Key Question 5 (Compliance)

Electronic Database Searches

The following databases have been searched for relevant information:

Name	Date limits	Platform/provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1990 through January 16, 2007	OVID
Cochrane Library	Through 2007 Issue 1	www.thecochranelibrary.com
Embase (Excerpta Medica)	1990 through January 24, 2007	OVID

Medline	1990 through January 16, 2007	OVID
PubMed (Premedline)	Premedline[sb] Searched January 15, 2007	www.pubmed.gov
TRIS Online (Transportation Research Information Service Database)	Through September 18, 2006	http://trisonline.bts.gov/search.cfm

Hand Searches of Journal and Nonjournal Literature

Journals and supplements maintained in ECRI's collections were routinely reviewed. Nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

Controlled Vocabulary Headings (MeSH, EMTREE, PsycINFO Subject Headings) and Keywords

Conventions:

$ = truncation character (wildcard) in OVID syntax
exp = "explodes" controlled vocabulary term. E.g. expands search to all more specific related terms in the vocabulary's hierarchy.
.de. = limit controlled vocabulary heading in OVID syntax
.fc. = form/content type (PsycINFO – OVID syntax)
.fs. =floating subheading in OVID syntax
.hw. = limit to heading word in OVID syntax
.mp. =combined search fields in OVID syntax (default if no fields are specified)
.pt. =publication Type in OVID syntax
.ti. =limit to title in OVID syntax
.tw. =limit to title and abstract fields in OVID syntax

Topic-specific Search Terms

Compliance
Adher$
Complian$
Non-adher$
Nonadher$
Patient compliance.de.

Outcome
Follow-up
Long-term
Longitudinal
Outcome$

Seizures

Convuls$
Epilepsy
Epilep$
Fits
Seizure$
seizures

Embase/Medline/Cinahl (English language, human)

Set Number	Concept	Search statement
1	Seizures	Exp epilepsy/ or exp seizures/ or (seizure$ or epilep$ or convuls$ or fits).ti.
2	Compliance	Patient compliance.de. or (complian$ or adher$ or non-adher$ or nonadher$)
3	Outcome	Outcome* or treatment outcome.de. or follow-up or longitudinal or long-term
4	Combine sets	1 and 2 and 3
5	Remove overlap	Remove duplicates from 4
6	Limit by publication type	5 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
7	Limit by study type	6 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebo or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study).de. or random$.hw. or random$.ti. or placebo$ or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham)) or latin square or ISRTCN)

PreMedline (PubMed)

Set Number	Concept	Search statement
1	Seizures	Epilepsy OR “convulsive disorder” OR “convulsive disorders” OR “seizure disorder” OR “seizure disorders” OR seizure*[ti])
2	Compliance	Compliance OR adher* OR non-adher* OR nonadher*
3	Combine sets	#1 AND #2
4	Limit	#3 AND (in process[sb] OR publisher[sb])

Search Strategies for Key Question 6 – AED Impact

Electronic Database Searches

The following databases have been searched for relevant information:

Name	Date limits	Platform/provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1990 through January 16, 2007	OVID
Cochrane Library	Through 2007 Issue 1	www.thecochranelibrary.com
Embase (Excerpta Medica)	1990 through January 24, 2007	OVID
Medline	1990 through January 16, 2007	OVID
PubMed	Premedline[sb]	www.pubmed.gov

(Premedline)	Searched January 15, 2007	
TRIS Online (Transportation Research Information Service Database)	Through September 18, 2006	http://trisonline.bts.gov/search.cfm

Hand Searches of Journal and Nonjournal Literature

Journals and supplements maintained in ECRI's collections were routinely reviewed. Nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

Controlled Vocabulary Headings (MeSH, EMTREE, PsycINFO Subject Headings) and Keywords

Conventions:

$ = truncation character (wildcard) in OVID syntax
exp = "explodes" controlled vocabulary term. E.g. expands search to all more specific related terms in the vocabulary's hierarchy.
.de. = limit controlled vocabulary heading in OVID syntax
.fc. = form/content type (PsycINFO – OVID syntax)
.fs. =floating subheading in OVID syntax
.hw. = limit to heading word in OVID syntax
.mp. =combined search fields in OVID syntax (default if no fields are specified)
.pt. =publication Type in OVID syntax
.ti. =limit to title in OVID syntax
.tw. =limit to title and abstract fields in OVID syntax

Topic-specific Search Terms

Drug therapy
Anticonvulsant$
Antiepileptic$
Antiseizure$
Dt.fs.

Outcome
Follow-up
Long-term
Longitudinal
Outcome.de.
Treatment outcome

Recurrence
Recur$

Recurrence
Relapse
Relaps$

Risk
Proportional hazard models.de.
Risk/
Risk$

Seizures
Convuls$
Epilepsy
Epilep$
Fits
Seizure$
Seizures

Embase/Medline/Cinahl (English language, human)

Set Number	Concept	Search statement
1	Seizures	Exp epilepsy/ or exp seizures/ or (seizure$ or epilep$ or convuls$ or fits).ti.
2	Risk	Exp risk/ or risk$.ti. or proportional hazard models.de. or proportional hazards model.de.
3	Drug therapy – systematic reviews	Exp *epilepsy/dt and (research synthesis or meta analysis or systematic review or meta-analy$ or meta analy$ or Cochrane.ti.)
4	Drug therapy	Dt.fs. or anticonvulsant$ or antiseizure$ or antiepileptic$
5	Recurrence	*recurrence/ or *relapse/ or recurrent disease.de. or *recurrence risk/ or (recur$ or relaps$).ti.
6	Outcome	Outcome* or treatment outcome.de. or follow-up or longitudinal or long-term
7	Combine sets	(1 and 2 and 4 and 5 and 6) or 3
8	Remove overlap	Remove duplicates from 7
9	Limit by publication type	8 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
10	Limit by study type	9 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebo or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study).de. or random$.hw. or random$.ti. or placebo$ or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham)) or latin square or ISRTCN)

Appendix B: Retrieval Criteria

Appendix B will list the retrieval criteria for each key question. An example of a small set of retrieval criteria are presented below.

Retrieval Criteria for Key Question 1

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash either directly (risk for a fatal or non-fatal crash) associated with epilepsy.
- Article must describe a study that includes a comparison group comprised of comparable subjects who do not have epilepsy.

Retrieval Criteria for Key Question 2

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Study must have reported on the time since last seizure.

Retrieval Criteria for Key Question 3

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Study must have reported on the time since last seizure.

Retrieval Criteria for Key Question 4

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Study must have reported on the time since last seizure.

Retrieval Criteria for Key Question 5

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must have addressed the issue of compliance

Retrieval Criteria for Key Question 6

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.

- Article may describe a study that attempted to evaluate the relationship between epilepsy and the following direct and indirect measures of driver safety:
  - Measures of driving-related performance (laboratory and experimental)
  - Measures of driving-related cognitive function
  - Measures of driving-related psychomotor function

Appendix C: Inclusion Criteria

Appendix C will lists the inclusion criteria for each of the six key questions addressed in this evidence report.

Inclusion Criteria for Key Question 1

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash associated with epilepsy.
- Article must compare the proportion of drivers with epilepsy who crashed (cases) with the proportion of comparable individuals without the disorder who did not crash (controls), or
- Article must compare the proportion of individuals with epilepsy among a group of drivers who crashed (cases) with the proportion of individuals with epilepsy among a comparable group of individuals who did not crash (controls)

Inclusion Criteria for Key Question 2

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that utilized a minimum of 80% adults (≥18 years).
- Article may be prospective or retrospective-with-consecutive enrollment
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted so as to avoid double-counting patients.
- Study must have reported on the time since last seizure.
- The minimum follow-up time of the study must have been at least one year.
- Studies of individuals on AEDs after surgery not considered (see Key Question 3).

Inclusion Criteria for Key Question 3

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.

- Article must describe a study that utilized a minimum of 80% adults (≥18 years).
- Article may be prospective or retrospective-with-consecutive enrollment
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted so as to avoid double-counting patients.
- Study must have reported on the time since last seizure.
- The minimum follow-up time of the study must have been at least one year.
- Studies of individuals on AEDs following surgery were eligible.

Inclusion Criteria for Key Question 4

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that utilized a minimum of 80% adults (≥18 years).
- Article may be prospective or retrospective-with-consecutive enrollment
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted so as to avoid double-counting patients.
- Study must have enrolled only individuals who had experienced a single, unprovoked seizure.
- Study must have reported on the time since last seizure.
- The minimum follow-up time of the study must have been at least one year.

Inclusion Criteria for Key Question 5

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that utilized a minimum of 80% adults (≥18 years).

Inclusion Criteria for Key Question 6

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.

- Article must have enrolled subjects aged ≥18.
- Article must have enrolled subjects who were receiving AED therapy for ≥ 6 months (this being considered for the purposes of this report to be chronic AED use).
- Article must have enrolled subjects who were seizure-free for a minimum of 1 year.[14]
- Article may describe a study that attempted to evaluate the relationship between epilepsy and the following direct and indirect measures of driver safety:
  - Measures of driving-related performance (laboratory and experimental)
  - Measures of driving-related cognitive function
  - Measures of driving-related psychomotor function
- Article must present data in a manner that will allow ECRI to calculate (directly or through imputation) effect size estimates and confidence intervals.

[14] For the purposes of FMCSA, individuals must be seizure free in order to drive a CMV.

Appendix D: Excluded Articles

Table D-1. Excluded studies (Key Question 1)

Reference	Year	Reason for exclusion
Bares et al.(201)	1997	Does not address Key Question 1. Looks at driving skill in individuals with epilepsy
Beaussart et al.(202)	1997	Series. No appropriate comparison group
Beghi et al.(203)	2001	Does not address Key Question 1. Study investigates risk ratio for any accident among individuals with epilepsy when compared to controls.
Bener et al.(204)	1996	Series. No appropriate comparison group
Berg et al.(205)	2000	Series. No appropriate comparison group
Cimbura et al.(206)	1982	Does not address Key Question 1. Looks at drug levels in fatally injured drivers
Constantinou et al.(207)	1990	Series. No appropriate comparison group
Drazkowski et al.(208)	2003	Does not address Key Question 1. Looks at change in crash incidence following the reduction of a driving restriction following seizure from 12 to 3 months
Fries et al.(209)	2005	Does not address Key Question 1. Survey of neurological disorders that resulted in an accident (any kind) requiring attention at a hospital. No comparison group.
Gastaut et al.(95)	1987	Does not address Key Question 1. Assesses type of seizure as a risk factor for crash. Data from study discussed in main body of evidence report
Hansotia et al.(210)	1994	Series. No appropriate comparison group. Looked at risk factors for crash. Epilepsy cohort same as that reported in study of Hansotia and Broste(88)
Hasegawa et al.(211)	1991	No comparison group. Survey of seizure types associated with crash (Q2).
Hashimoto et al.(212)	1991	Series. No appropriate comparison group
Herons et al.(213)	1956	Not a study. Review/commentary article
Hormia et al.(214)	1960	?
Krause et al.(94)	1991	Does not address Key Question 1. Assesses risk factors associated with crash. Data from study discussed in main body of evidence report
Kugler et al.(215)	1991	Does not address Key Question 1. Looks at effect of sleep deprivation and EEG findings
Lennox et al.(216)	1958	Not a study. Review/commentary article
McGlone et al.(217)	1986	Does not address Key Question 1. Looks at AED levels among individuals presenting at an accident and emergency unit.
Millingen et al.(218)	1976	Series. No appropriate comparison group
Norman et al.(219)	1960	Not a study. Review/commentary article
Parsons et al.(220)	1986	Does not address Key Question 1. Survey of occurrence of fits and loss of consciousness while driving.
Rajna et al.(221)	2003	Series. No appropriate comparison group
Seneviratne et al.(222)	1999	?
Spudis et al.(223)	1986	?
Stanaway et al.(163)	1983	Series. No appropriate comparison group
Takeda et al.(224)	1991	Series. No appropriate comparison group

Reference	Year	Reason for exclusion
Takeda et al.(225)	1992	Series. No appropriate comparison group
Taylor et al.(226)	1995	?
Tiamkao et al.(227)	2006	Series. No appropriate comparison group
Trenite et al.(228)	1987	Does not address Key Question 1. Study of EEG and driving behavior.
Van den Broek et al.(229)	2004	Does not address Key Question 1. Study investigates risk ratio for any accident among individuals with epilepsy when compared to controls.
Van der Lugt(230)	1975	Does not address Key Question 1. Examined incidence of crashes caused by epilepsy. Compared type and severity of accident with accidents experienced by individuals without epilepsy. No relevant comparison group.
Wick et al.(231)	2004	Not a study. Review/commentary article

Table D 2. Excluded studies (Key Question 2)

Reference	Year	Reason for Exclusion
American Epilepsy Society(16)	2004	Reference source
World Health Organization(19)	2005	Reference source
Wilby et al.(182)	2005	Reference source
Aktekin et al.(105)	2006	Time since last seizure not reported
Annegers et al.(104)	1979	Time since last seizure not reported
Annegers et al.(232)	1995	Background information source
Anonymous(112)	1996	Background information source
Anonymous(233)	1997	Background information source
Baumhackl et al.(234)	1994	Background information source
Bazil(235)	2004	Background information source
Britton(236)	2002	Background information source
Cardoso et al.(108)	2003	Time since last seizure not reported
Chadwick(237)	1999	Time since last seizure not reported
Chadwick and Scherokman(238)	1991	Study not available
Chadwick et al.(111)	1996	Time since last seizure not reported
Cockerell et al.(103)	1995	Time since last seizure not reported
Davis et al.(239)	1994	Background information
Dichter(240)	1992	Background information
Hauser(241)	1992	Background information
Hauser et al.(242)	1993	Background information
Kalita et al.(107)	2005	Time since last seizure not reported
Keranen and Riekkinen(243)	1993	Background information
Kilpatrick(244)	2004	Background information

Reference	Year	Reason for Exclusion
Kim(245)	1995	Background information
Kotsopoulos et al.(145)	2005	Background information
Lamdhade and Taori(246)	2002	Time since last seizure not reported
LaRoche and Helmers(20)	2004	Background information
Leppik et al.(247)	2006	Time since seizure not reported
Lhatoo et al.(248)	2001	Background information
Lossius et al.(110)	1999	Time since last seizure not reported
MacDonald et al.(249)	2000	Background information
MacDonald and Purdy(250)	1986	Review
Medical Research Council Antiepileptic Drug Withdrawal Study Group(118)	1991	Time since last seizure not reported
Medical Research Council Antiepileptic Drug Withdrawal Study Group(116)	1993	Time since last seizure not reported
Quality Standards Subcommittee of the American Academy of Neurology(251)	1996	Time since last seizure not reported
Mukasa et al.(115)	1994	Time since last seizure not reported
Nakazawa et al.(113)	1995	Time since last seizure not reported
Overweg(252)	1995	Background information
Perucca and Meador(166)	2005	Reference source
Ranganathan and Ramaratnam(253)	2006	Time since last seizure not reported
Ranheim et al.(254)	1965	Background information
Sackellares et al.(255)	2006	Model too specific for adaptation to key question
Sander(96)	2003	Background information
Sander(31)	2005	Background information
Schmidt and Loscher(256)	2005	Review
Sillanpaa and Schmidt(106)	2006	Time since last seizure not reported
Sillanpaa and Shinnar(257)	2005	Background information
Specchio and Beghi(258)	2004	Background information

Reference	Year	Reason for Exclusion
Specchio and Beghi(259)	2004	Background information
Specchio et al.(109)	2002	Time since last seizure not reported
Tanaka et al.(117)	1992	Time since last seizure not reported
Temkin(260)	2001	Not relevant - meta-analysis of seizure prevention trials
Uesugi et al.(261)	1994	Time since last seizure not reported
Verrotti et al.(262)	2003	Time since last seizure not reported
Wingerchuk and Sirven(263)	2005	Review

Table D-3 Excluded studies (Key Question 3)

Reference	Year	Reason for exclusion
Assaf et al.(264)	1999	Does not provide relevant time-to-event data
Berkovic et al.(265)	1995	Does not provide relevant time-to-event data
Blume et al.(266)	1997	Does not provide relevant time-to-event data
Brekelmans et al.(267)	1998	Does not provide relevant time-to-event data
Burneo et al.(136)	2005	Does not provide relevant time-to-event data
Chung et al.(268)	2005	Does not provide relevant time-to-event data
Clusmann et al.(269)	2002	Does not provide relevant time-to-event data
Ficker et al.(270)	1999	Does not provide relevant time-to-event data
Kilpatrick et al.(139)	1999	Does not provide relevant time-to-event data
Kim et al.(127)	2005	Does not provide relevant time-to-event data
Manno et al.(271)	1994	Does not provide relevant time-to-event data
McIntosh et al.(272)	2005	Does not provide relevant time-to-event data
Newberg et al.(273)	2000	Does not provide relevant time-to-event data
Orbach et al.(51)	2001	Does not provide relevant time-to-event data
Radhakrishnan et al.(274)	2003	Does not provide relevant time-to-event data
Redhackrishnan et al.(125)	1998	Does not provide relevant time-to-event data
Salanova et al.(138)	2002	Does not provide relevant time-to-event data
Sirven et al.(275)	1997	Does not provide relevant time-to-event data
Spencer et al.(276)	2003	Superseded by another article(126)
Srikiljvi et al.(277)	2003	Does not provide relevant time-to-event data
Stavem et al.(137)	2004	Does not provide relevant time-to-event data
Sylaja et al.(278)	2004	Does not provide relevant time-to-event data
Wyler et al.(36)	1995	Does not provide relevant time-to-event data

Table D-4. Excluded studies (Key Question 4)

Study	Year	Reason for exclusion
Annegers et al.(279)	1986	Fewer than 90% of enrolled individuals were adults
Beghi et al.(280)	1992	Secondary publication of the FIRST trial
Bora et al.(281)	1995	Fewer than 90% of enrolled individuals were adults
Camfield et al.(282)	2002	All individuals were children at the time of the single unprovoked seizure, and authors did not investigate factors predicting recurrence.
Chadwick et al.(111)	1996	Individuals had had more than one seizure prior to enrollment
Chadwick et al.(283)	1991	Letter - comment
Cleland et al.(284)	1981	Seizures were not unprovoked in some individuals
Das et al.(285)	2000	Fewer than 90% of enrolled individuals were adults
Dashieff et al.(286)	1987	Letter - comment
Donselaar et al.(287)	1992	Secondary publication of van Donselaar 1991
Elwes et al.(288)	1985	Fewer than 90% of enrolled individuals were adults, and authors did not investigate any factors predicting seizure recurrence
FIRST et al.(289)	1993	FIRST trial; fewer than 90% of enrolled individuals were adults
Fisher et al.(290)	1987	Letter - comment
Gupta et al.(291)	1993	Fewer than 90% of enrolled individuals were adults
Hart et al.(292)	1990	Fewer than 90% of enrolled individuals were adults, and did not report whether seizures were unprovoked
Hart et al.(293)	1986	Review article
Hauser et al.(294)	1998	Fewer than 90% of enrolled individuals were adults
Hauser et al.(140)	1990	Overlapping individuals with Hauser 1998
Hauser et al.(295)	1986	Review article
Hauser et al.(296)	1982	Overlapping individuals with Hauser 1990 and Hauser 1998
Hauser et al.(142)	2002	Overlapping individuals with Hauser 1998
Hui et al.(297)	2001	Fewer than 90% of enrolled individuals were adults
Hyllested et al.(298)	1963	Some individuals had had more than one seizure when enrolled into the study, and authors did not report how many individuals' seizures were unprovoked
Kawkabani et al.(299)	2004	Only ~22% of individuals had had an unprovoked seizure, and no recurrence data were reported for this subgroup of individuals
Kho et al.(300)	2006	Fewer than 90% of enrolled individuals were adults, and some individuals seizures were not unprovoked.
Kim et al.(301)	2006	Secondary publication of the MESS trial
King et al.(302)	1998	Fewer than 90% of enrolled individuals were adults, and some individuals had had 2+ prior seizures.
Kotsopoulos et al.(145)	2006	Incidence study; some individuals seizures were not unprovoked.
Leone et al.(303)	2006	Secondary publication of the FIRST trial
Lindsten et al.(304)	2001	Same individuals as Lindsten 2001(305)
Lindsten et al.(305)	2001	Some individuals had had more than one seizure when enrolled into the study
Madhusudanan et al.(146)	2000	Review article
Marson et al.(306)	2005	MESS trial; fewer than 90% of individuals were adults'
Marson et al.(98)	2006	Secondary publication of the MESS trial

Study	Year	Reason for exclusion
Martinovic et al.(307)	1997	Fewer than 90% of enrolled individuals were adults
Musicco et al.(308)	1997	Secondary publication of the FIRST trial
Reynolds et al.(280)	1988	Letter - comment
Saunders et al.(309)	1975	Did not report whether seizures were unprovoked
Thomas et al.(310)	1959	Did not report whether seizures were unprovoked, and fewer than 90% were adults

Table D-5. Excluded studies (Key Question 5)

Reference	Year	Reason for Exclusion
Abduljabbar et al.(311)	1998	Study included all patients over 12 years of age and data could not be separated out for adults and children.
Adamolekun et al.(312)	1999	Does not provide relevant data
Aldenkamp et al.(313)	1987	Not relevant – didn't measure compliance
Aldenkamp et al.(314)	1995	Not relevant – didn't measure compliance
American Epilepsy Society(16)	2004	Background only
Barrett et al.(315)	1997	Unable to locate.
Beaussart et al.(202)	1997	Measured compliance with self-report, not serum.
Beenen et al.(316)	1999	Not relevant – didn't measure compliance
Begley and Beghi(317)	2002	Background only
Beran et al;(318)	1985	Not relevant to study question
Bill et al.(319)	1997	Not relevant, trial comparing efficacy of two medications, measured compliance with serum concentration but never reported results or its relationship with seizure rate.
Bittencourt et al.(320)	1992	Not relevant – didn't measure compliance
Blum(99)	1998	Background only
Boon et al.(321)	2002	Not relevant, dose-response study, measured compliance with pill count, not serum
Bootsma(322)	2006	Not relevant – didn't report on seizure
Brodie et al.(323)	1995	Not relevant, trial comparing efficacy of two medications, withdrew patients from trial if they were noncompliant (measured through pill counts and serum concentration).
Brodie et al(324)	1999	Not relevant, trial comparing efficacy of two medications.
Buck et al.(325)	1997	Measured compliance with self-report, not serum.
Burton et al.(326)	1997	Not relevant – didn't measure compliance
Chandra et al.(168)	1993	Measured non-compliance versus sub-therapeutic dosing, but did not report on seizure.
Cochrane et al.(327)	1998	Background only
Constantinou et	1990	Did not report by what method compliance was measured.

Reference	Year	Reason for Exclusion
al.(207)		
Couldridge(328)	2001	Not relevant, narrative review only of information/counseling needs of epileptics
Cramer et al.(161)	1989	Study primarily examined relationship between MEMS and seizures. It also looked at relationship between serum levels and seizures but presented select data in the form of case reports only.
Cramer et al.(329)	1990	Study primarily examined compliance, as measured by MEMS, and its relationship to intervals between clinic visits. It also measured serum drug levels, but did not examine seizure occurrence at all.
Cramer et al(330)	2002	Measured compliance with self report, not serum.
Dawkins et al.(331)	1993	Not relevant
Dodrill et al.(332)	1999	Not relevant – didn't measure compliance
Dodrill et al.(333)	1997	Not relevant – didn't measure compliance
Dorland's Illustrated Medical Dictionary(334)	1974	Background only – for definitions
Doughty et al.(335)	2003	Measured compliance with self-report, not serum.
Dowse and Futter(336)	1991	Not relevant.
Driessen et al(337)	1977	Study included children.
Drislane(338)	1994	Not relevant.
Duncan et al.(102)	2006	Background only
Dutta et al.(339)	2006	Not relevant – didn't measure compliance
Edwards(340)	1974	Background only
Eisler and Mattson(341)	1975	Unable to locate article.
Faught et al.(342)	2004	Not relevant.
Feldman et al.(343)	1976	Examined actual drug serum levels and expected drug serum levels in a group of epileptics who were seizure free for 2 years prior to the trial and whom the physician believed to be compliant with their AEDs. Did not report on seizures at all.
Fisher et al(344)	2000	Background only
Freeman(345)	1997	Not relevant.
Gambardella et al(346)	1994	Not relevant – didn't measure compliance
Garnett et al.(152)	2000	Background only
Gillham et al.(347)	1993	Add-on trial, examining effects on cognitive function, measured compliance with pill count, not serum.
Gillham et al(348)	2000	Not relevant, trial comparing efficacy and QOL (SEALS) in patients newly diagnosed with epilepsy on two competing medications, did not measure compliance, just compared patients who remained in trial versus those who withdrew from trial on SEALS scores.
Gilliam et al.(349)	1998	Not relevant, switching medication trial.
GlaxoSmithKline(350)	2000	Unable to locate.
Gomes et al.(351)	1998	Measured compliance with self report, not serum.
Gomez et al.(352)	1998	Study included children.
Graves et al(353)	1988	Not relevant; add-on, crossover trial which included only highly compliant subjects.
Haynes et al.(354)	2005	Not relevant.

Reference	Year	Reason for Exclusion
Helgeson et al.(355)	1990	Relevant to topic, but less than 10 patients per research arm was included in the part of the study which had blood serum levels measured.
Irving et al.(356)	1999	Study included only patients presenting with seizure; included a mixed population: epilepsy, first time seizure, status epilepticus, and pseudoseizure.
Jones et al.(357)	2006	Measured compliance with self-report, not serum.
Juni et al.(358)	2002	Background only – regarding English only articles for inclusion
Kalviainen et al.(359)	1996	Not relevant, looked at effect of drug on cognitive scores
Kalvianen et al.(359)	1996	Not relevant – didn't measure compliance
Kemp et al.(170)	2007	Not relevant – didn't report on seizure
Kobau and Dilorio(360)	2003	Not relevant – examined the relationship between AED compliance (self-report) and compliance with other healthful measures, such as getting 7-9 hours of sleep per night as well as patient beliefs about what outcomes were likely from both types of compliance.
Koskiniemi et al.(361)	1998	Not relevant – didn't measure compliance
Krueger et al.(160)	2005	Not relevant, narrative review of adherence technique trials for all disorders
Krueger et al.(154)	2003	Not relevant, narrative review of adherence technique trials for all disorders
Krumholz et al.(362)	1989	Study included children and a mixed seizure population.
Leach et al.(363)	1997	Not relevant – didn't measure compliance
Leppik(155)	1990	Background only
Leppik et al.(167)	1979	Measured compliance but did not report on its relationship to seizure frequency.
Lhatoo et al.(364)	2000	Not relevant.
Lings(365)	2002	Non-English language article
Lisk(366)	1992	Not relevant.
Liu et al.(159)	2003	Tested effectiveness of AED information pamphlets on patient knowledge of AEDs and compliance. Measured compliance with self report and serum pre- and post-intervention but did not report on its relationship to seizure frequency.
Loiseau et al.(367)	1990	Not relevant, add on trial, excluded patients with a history of NC at outset, measured compliance during trial with pill counts.
Long(157)	2000	Background only
Luhdorf et al(368)	1986	Study included only patients presenting with seizure.
MacDonald et al.(250)	1986	Background only
Macphee et al.(369)	1986	Not relevant – didn't measure compliance
Mani et al.(370)	2001	Measured compliance with self report, family interviews and tablet counts, but not serum. Included adults and children.
Manni et al.(371)	1993	Not relevant – didn't measure compliance
Martin et al.(153)	2005	Background only
Maton(372)	1998	Unable to locate.
Mattson et al.(373)	1988	Not relevant.

Reference	Year	Reason for Exclusion
McGloane and Pritty(217)	1986	Study included only patients presenting with seizure.
McKee et al.(374)	1993	Add-on trial, measured compliance with pill count, not serum.
McKee et al.(375)	1994	Not relevant – didn't measure compliance
Medical Research Council Antiepileptic Drug Withdrawal Study Group(118)	1991	Not relevant; study includes children.
Moher et al.(376)	2000	Background only – regarding English only articles for inclusion
Nichols et al(377)	1993	Background only
Nieto-Barrera et al.(378)	2001	Not relevant, trial comparing efficacy and rate of withdrawal from trial for two competing medications, in newly diagnosed patients; did measure compliance but with self report and did not report its relationship to seizure.
Nousiainen et al.(379)	2000	Not relevant – didn't measure compliance
Ogbuokiri et al.(380)	1992	Not relevant – didn't measure compliance
Ogunniyi et al.(381)	1998	Measured compliance with self-report and family interviews, not serum.
Otani(382)	1995	Measured compliance with self-report and family interviews. This study also did serum blood draws used this information to determine how pregnancy itself can affect seizure rates; they excluded AED levels that suggested non-compliance from the analysis.
Perucca et al.(166)	2005	Background only
Peterson(156)	1982	Measured compliance with self-report, not serum.
Peytchev(162)	1997	Background only
Prevey et al.(383)	1996	Not relevant – didn't measure compliance
Pulliainen et al.(384)	1994	Not relevant – didn't measure compliance
Read et al.(385)	1998	Not relevant – didn't measure compliance
Reunanen et al(386)	1996	Not relevant, trial comparing efficacy of two medications, withdrew patients from trial if they were noncompliant (measured through self-report, pill counts and serum concentration).
Rimmer and Richens(387)	1984	Not relevant, add on trial, measured compliance with pill count, not serum
Risdale et al(388)	1997	Not relevant
Rodin et al.(389)	1989	Not relevant – didn't measure compliance
Roman et al.(390)	1996	Not relevant – didn't measure compliance
Runge et al(391)	1996	Measured compliance on several factors combined, including sleep deprivation, alcohol consumption, pill counts, self report, family interview and drug serum level.
Sachdeo et al.(392)	1998	Unable to locate.
Sander et al(393)	1990	Not relevant, add-on trial.
Satetu et al.(394)	1984	Not relevant – didn't measure compliance
Schachter et al.(395)	1995	Add-on trial, measured compliance with self report, not serum.
Schmidt et al.(396)	2000	Background only
Schmidt et al.(397)	1983	Measured compliance with self-report, not serum.
Schmidt et	1993	Unable to locate.

Reference	Year	Reason for Exclusion
al(398)		
Schmidt et al(158)	1988	Two trials: one relevant but included children; second measured compliance by self report, not serum.
Scott(399)	1984	Expert opinion article
Scottish Intercollegiate Guidelines Network(400)	2003	Background only
Semah et al.(401)	1994	Not relevant – didn't measure compliance
Smith et al(402)	1993	Not relevant, Add-on trial
Snow et al.(403)	1991	Study included only patients presenting with seizure.
Specht et al.(169)	2003	Study included children.
Stanaway et al.(404)	1985	Measured compliance on several factors combined, including self report, saliva concentrations, and time between prescription refills.
Stanaway et al.(163)	1983	Measured compliance with saliva samples, not blood serum
Steiner et al(405)	1999	Not relevant, measured compliance with pill count and withdrew NC from trial
Stores et al.(406)	1992	Not relevant – main purpose was to assess cognitive effects of drugs and participants were children
Sundqvist et al.(407)	1999	Not relevant – didn't measure compliance
Sveinbjornsdottir et al.(408)	1994	Not relevant – didn't measure compliance
Takaki et al(409)	1985	Study included children.
Tan and Bruni(410)	1986	Mixed population and final analysis based on treatment arms that fell below the requisite 10 subjects.
Tan et al.(411)	2005	Measured compliance with self-report, not serum. This study did do serum blood draws but only reported on those patients with sub-therapeutic levels who claimed to be compliant with medications. It also included status epilepticus patients.
Tanganelli and Regesta(412)	1996	Not relevant, cross over trial, excluded NC patients
Tassinari et al.(413)	1987	Add-on trial, measured compliance with pill count, not serum.
Thijs et al.(414)	1998	Not relevant.
Thorbecke(415)	1988	Measured compliance with missed appointments, not blood serum
Tiamkao et al.(416)	2006	Study included only patients presenting with seizure; and study included a mixed population of children and patients with status epilepticus, first seizures, etc.
Trostle(417)	1988	Measured compliance with self report and chart notes, not serum.
Troupin et al.[(418)	1977	Not relevant – didn't measure compliance
Wagner et al.(151)	2007	Background only
Wakamoto et al.(419)	2000	Measured compliance with self-report, not serum.
Wang et al(420)	2006	Measured compliance with pill counts, not blood serum
WHO(421)	1997	Background only
Wilby et al.(422)	2005	Not relevant

Reference	Year	Reason for Exclusion
Williams et al.(164)	2002	Measured compliance with hair samples, not serum.
Williams et al.(165)	1997	Examined a compliant populations (in-patients) in terms of hair concentration of drug, did not report on seizure.

Table D-6. Excluded studies (Key Question 6)

Reference	Year	Reason for Exclusion
Epilepsy Foundation(423)	2006	Background information only. Does not meet inclusion criteria
International League Against Epilepsy(424)	2007	Background information
Satishchandra et al(425)	2001	Reference
Disability law: inability to drive to work not a disability, court rules. LEGAL EAGLE EYE NEWSLETTER NURS PROF(426)	2001	Background information
Braun and Christ(427)	2002	Reference
Charlton et al(428)	2004	Reference
Commercial insight: anticonvulsants. How to avoid a brand identity crisis by choosing your battlegrounds carefully.[internet] Datamonitor(429)	2004	Background information
American Epilepsy Society(15)	2004	Background information
American Epilepsy Society(430)	2004	Background information
American Epilepsy Society(16)	2004	Background information
Ramaekers et al.(431)	2004	Background information
American Epilepsy Society(22)	2004	Background information
Elan Pharma International Ltd.(32)	2004	Background information
World Health Organization (WHO)(19)	2005	Background information
U.S. Department of Transportation, Federal Railroad Administration. National Technical Information Service (NTIS)(432)	2005	Background information
U.S. Department of	2005	Background information

Reference	Year	Reason for Exclusion
Transportation, Federal Railroad Administration. National Technical Information Service (NTIS)(433)		
U.S. Department of Transportation, Federal Railroad Administration. National Technical Information Service (NTIS)(434)	2005	Background information
U.S. Department of Transportation, Federal Railroad Administration. National Technical Information Service (NTIS)(435)	2005	
Wilby et al.(182)	2005	Background information
Laboratory. [internet]University of Maastricht(189)	2005	Background information
Epilepsy Foundation(30)	2006	Background information
National Traffic Highway Safety Administration(436)	2006	Background information
Aikia et al.(437)	2006	Excluded via Inclusion/Exclusion criteria
Aikia et al.(438)	1992	Excluded via Inclusion/Exclusion criteria
Akaho(439)	1996	Excluded via Inclusion/Exclusion criteria
Aldenkamp(440)	2001	Review/Reference
Aldenkamp et al.(441)	1994	Excluded via Inclusion/Exclusion criteria
Aldenkamp et al.(313)	1987	Excluded via Inclusion/Exclusion criteria
Aldenkamp et al.(442)	2000	Excluded via Inclusion/Exclusion criteria
Aldenkamp and Baker(443)	1997	Excluded via Inclusion/Exclusion criteria
Aldenkamp and Bodde(192)	2005	Reference
Aldenkamp et al.(444)	2003	Review/Reference
Aldenkamp(445)	1998	Excluded via Inclusion/Exclusion criteria
Aldenkamp and Vermeulen(446)	1995	Review/Reference
Allen(447)	2003	Background
Andermann et al.(448)	1988	Review
Andrewes et al.(449)	1986	Excluded via Inclusion/Exclusion criteria
Andrewes et al.(450)	1990	Drug comparison not appropriate for topic

Reference	Year	Reason for Exclusion
Andrewes et al.(451)	1984	Excluded via Inclusion/Exclusion criteria
Annegers et al.(232)	1995	Topic for Neurology II report
Anonymous(112)	1996	Background
Armon et al.(452)	1996	Excluded via Inclusion/Exclusion criteria
Ashton(453)	1983	Background
Baker and Marson(454)	2001	Reference
Banks and Beran(455)	1991	Excluded via Inclusion/Exclusion criteria
Barcs et al.(201)	1997	Background
Baron(456)	2005	Background
Baumhackl et al.(234)	1994	Background
Bautista and Wludyka(457)	2006	Background
Bazil(235)	2004	Background
Beaussart et al.(202)	1997	Background
Beghi et al.(203)	2002	Background
Beghi et al.(458)	2000	Background
Begley et al.(459)	1999	Background
Begley and Beghi(317)	2002	Background
Begley et al.(54)	2000	Background
Bell(460)	2006	Excluded via Inclusion/Exclusion criteria
Bell et al.(461)	2002	Excluded via Inclusion/Exclusion criteria
Bell et al.(462)	2005	Excluded via Inclusion/Exclusion criteria
Ben-Menachem(463)	2004	Background
Benbadis et al.(464)	2000	Background
Beran(465)	1982	Background
Beran(466)	1997	Background
Beran(467)	2002	Background
Beran(468)	2005	Background
Berent et al.(469)	1987	Background
Berg and Engel(470)	1999	Background
Berg and Engel(471)	2006	Background
Berg et al.(472)	2000	Background
Berkovic(473)	2000	Background
Berkovic(474)	2001	Background
Besag(475)	2001	Background
Besag(476)	2006	Background
Bhatt et al.(477)	2005	Background
Bielen et al.(478)	1999	Background

Reference	Year	Reason for Exclusion
Binnie(479)	2003	Background
Binnie(480)	1990	Background
Bittencourt et al.(481)	1993	Excluded via Inclusion/Exclusion criteria
Bittencourt et al.(320)	1992	Background
Black(482)	2003	Background
Black and Lai(483)	1997	Background
Block and Fisher(484)	1999	Background
Blum et al.(485)	2006	Excluded via Inclusion/Exclusion criteria
Blum(99)	1998	Background
Blume et al.(486)	2007	Background
Boggs(487)	1997	Background
Bonanni et al.(488)	2001	Excluded via Inclusion/Exclusion criteria
Bonanni et al.(489)	2004	Background
Bonanni et al.(490)	1997	Background
Boyle et al.(491)	2004	Background
Bremner et al.(492)	2005	Excluded – may be used for Neurology II report
Broughton et al.(493)	1984	Background
Brown and Bird(494)	2002	Background
Browne et al.(495)	1989	Excluded via Inclusion/Exclusion
Brunbech and Sabers(496)	2002	Review
Bruni(497)	1994	Review
Burton and Harden(326)	1997	Excluded via Inclusion/Exclusion criteria
Caicoya and Serratosa(498)	2006	Background
Cary et al.(499)	1983	Case report
Cereghino and Fulghum(500)	1972	Excluded – topic for Neurology II report
Chadwick(501)	1994	Background
Chadwick(502)	2001	Excluded via Inclusion/Exclusion criteria
Chassiakos(503)	2003	Background
Chaudhry et al.(504)	1992	Excluded – drug not used in US
Cheuk and Wong(505)	2006	Background
Chopra et al.(506)	1993	Background
Cicolin et al.(507)	2006	Excluded – topic for Neurology II report
Cimbura et al.(206)	1982	Background
Cochrane et al.(327)	1998	Background
Cohen et al.(508)	1985	Excluded via Inclusion/Exclusion criteria
Constantinou and Gubbay(207)	1990	Background

Reference	Year	Reason for Exclusion
Cornaggia et al.(509)	2006	Background
Cosbey(510)	1986	Background
Craig and Tallis(511)	1994	Excluded via Inclusion/Exclusion criteria
Cramer et al.(512)	2003	Review
Crouch et al.(513)	1983	Background
Curran and Java(514)	1993	Excluded via Inclusion/Exclusion criteria
Daban et al.(515)	2006	Excluded – topic for Neurology II report
Dalby(516)	1975	Background
Dalrymple and Appleby(517)	2000	Background
Dasgupta et al.(518)	1982	Background
Davis et al.(239)	1994	Review
De Gier(519)	1984	Background
Deckers et al.(520)	1997	Background
Delcker et al.(521)	1997	Excluded via Inclusion/Exclusion criteria
Devinsky(522)	1995	Review
Dilorio et al.(523)	2003	Excluded via Inclusion/Exclusion criteria
Dijkstra et al.(524)	1992	Drug not available in US
Dixit et al.(205)	1996	Excluded via Inclusion/Exclusion criteria
Dodrill(198)	1988	Review
Dodrill(60)	1992	Review
Dodrill et al.(332)	1999	Excluded via Inclusion/Exclusion criteria
Dodrill et al.(525)	1998	Excluded via Inclusion/Exclusion criteria
Dodrill and Arnett(333)	1997	Excluded via Inclusion/Exclusion criteria
Dodrill and Temkin(526)	1989	Review
Dodrill and Troupin(527)	1977	Excluded via Inclusion/Exclusion criteria
Dodrill and Wilensky(528)	1992	Review
Donchin et al.(529)	2002	Background
Drane and Meador(530)	1996	Review
Drane and Meador(174)	2002	Review
Drane et al.(531)	2006	Background
Drazkowski(532)	2003	Background
Duncan et al.(533)	1990	Background
Edwards(340)	1974	Excluded – topic for Neurology II report
Eisenschenk and Gilmore(534)	1999	Background
Evans and Gualtieri(535)	1985	Review
Faught et al.(342)	2004	Excluded via Inclusion/Exclusion criteria

Reference	Year	Reason for Exclusion
Finucane(536)	1999	Background
Finucane(537)	1999	Background
Fisher and Blum(538)	1995	Review
Fisher and Krumholz(539)	1988	Background
Fisher et al.(540)	1994	Background
Fisher et al.(344)	2000	Background
Forney(541)	1973	Background
Forsgren et al.(542)	1996	Background
Fortenberry et al.(543)	1986	Excluded – topic for Neurology II report
Fountain et al.(544)	1983	Background
Frankenburg et al.(545)	1988	Excluded via Inclusion/Exclusion criteria
French et al.(546)	2001	Review
Fries et al.(209)	2005	Background
Fritz et al.(547)	2005	Excluded via Inclusion/Exclusion criteria
Gadoth et al.(548)	2002	Background
Gallassi et al.(549)	1987	Excluded via Inclusion/Exclusion criteria
Gallasi et al.(550)	1988	Excluded via Inclusion/Exclusion criteria
Gallassi et al.(195)	1990	Review
Garvin(551)	1979	Background
Gastaut and Zifkin(95)	1987	Background
Gates(176)	2000	Background
George(552)	2000	Background
Gerbo(553)	2004	Background
Gibson(554)	1983	Background
Gigli et al.(555)	1996	Excluded via Inclusion/Exclusion criteria
Gigli et al.(556)	1997	Excluded – topic not relevant
Gillham et al.(557)	1996	Background
Gillham et al.(558)	2000	Background
Gillham et al.(559)	1991	Excluded via Inclusion//Exclusion criteria
Gillham et al.(560)	1988	Background
Gillham et al.(561)	1990	Excluded via Inclusion//Exclusion criteria
Glasgow(562)	1979	Background
Goldberg and Burdick(563)	2001	Review
Grattan and Jeffcoate(564)	1968	Background
Grazia et al.(565)	1995	Excluded – topic not relevant
Groselj(566)	1997	Background
Gualtieri and Johnson(567)	2006	Drug comparison not appropriate for topic
Guiden(568)	2003	Background
Hamilton et al.(569)	1993	Excluded via inclusion/exclusion criteria

Reference	Year	Reason for Exclusion
Harden et al.(570)	1999	Excluded – topic not relevant
Harding et al.(571)	1985	Excluded via inclusion/exclusion criteria
Harvey and Hopkins(572)	1983	Excluded – topic not relevant
Hashimoto(573)	1994	Background
Hashimoto et al(212)	1991	Background
Hauser(241)	1992	Background
Hauser et al.(242)	1993	Background
Hauser and Lee(142)	2002	Background
Heaney(574)	1999	Background
Helbach(575)	1991	Background
Helmstaedter and Kockelmann(576)	2006	Background
Helmstaedter and Kurthen(577)	2001	Background
Helmstaedter et al.(578)	1993	Background
Herner et al.(579)	1966	Background
Hierons(213)	1956	Background
Hindmarch(580)	1995	Excluded – topic not relevant
Hindmarch et al.(581)	2005	Excluded – topic not relevant
Hindmarch et al.(179)	2005	Excluded – topic not relevant
Hirsch and Genton(582)	2003	Background
Hirsch et al.(583)	2003	Background
Hocking(584)	2003	Background
Hockings et al.(585)	1986	Background
Holden et al.(586)	2005	Background
Hopkins and Scrambler(587)	1977	Background
Hughes and Devinsky(588)	1994	Background
Hulihan(25)	2007	Background
Husain et al.(589)	2002	Background
Ieiri et al.(590)	1992	Excluded via Inclusion/Exclusion criteria
Inoue et al.(591)	2004	Background
Iudice et al.(592)	2002	Excluded – topic not relevant
Jeavons et al.(593)	1971	Background
Jeffery et al.(594)	1996	Background
Jenssen et al.(23)	2006	Background
Jha et al(595)	1992	Excluded via Inclusion/Exclusion criteria
Jokeit et al.(596)	2005	Background
Jokeit et al.(597)	2001	Background
Kalvianen(598)	1999	Background

Reference	Year	Reason for Exclusion
Kalvianen(599)	2001	Background
Kalvianen et al.(359)	1996	Excluded via Inclusion/Exclusion criteria
Kanner et al.(600)	2003	Background
Kaplan(601)	1999	Excluded – topic not relevant
Kasteleijn-Nolst et al.(228)	1987	Background
Kasteleijn-Nolst et al.(602)	2005	Background
Kay(180)	2001	Background
Kendrick et al.(603)	1993	Background
Kent et al.(604)	2006	Background
Keranen and Riekkinen(243)	1993	Background
Ketter et al.(605)	1999	Background
Kim(245)	1995	Background
King et al.(606)	1992	Background
Kingham(607)	1994	Background
Kipervasser et al.(608)	2004	Excluded – topic not relevant
Kisacanin et al.(609)	2000	Background
Kockelmann et al(610)	2004	Excluded via Inclusion/Exclusion criteria
Koh et al.(611)	2003	Background
Koplan(612)	1988	Background
Kotsopoulos et al.(145)	2005	Background
Kotsopoulos et al.(613)	2001	Background
Kozena et al.(614)	1997	Background
Krauss et al.(56)	2001	Background
Krumholz(615)	1994	Review
Krumholz et al.(81)	1991	Review
Kudoh and Matsuki(616)	2000	Background
Kugler et al.(215)	1991	Background
Kuhl et al.(617)	1967	Excluded – topic for Neurology II report
Kuitunen et al.(618)	1990	Background
Kuruvilla(619)	1994	Background
Kwan and Brodie(620)	2001	Background
Kwan and Sander(97)	2004	Background
Landau(621)	1979	Background
Langfitt(622)	2000	Background
Larkin et al.(623)	1989	Excluded via Inclusion/Exclusion criteria
LaRoche and Helmers(20)	2004	Review

Reference	Year	Reason for Exclusion
Leach et al.(363)	1997	Excluded via Inclusion/Exclusion criteria
LeBlang(624)	1979	Background
Lee et al.(625)	2006	Excluded via Inclusion/Exclusion criteria
Lee et al.(626)	2003	Excluded via Inclusion/Exclusion criteria
Legros and Bazil(627)	2003	Background
Lennox(216)	1956	Background
Levy(628)	2002	Review
Lhatoo et al.(629)	2000	Background
Lindsten et al.(630)	2002	Background
Lindsten et al.[#451808	2003	Background
Linnoila and Mattila(631)	1973	Excluded – drugs examined not appropriate
Loring et al.(632)	2000	Background
Loring and Meador(175)	2001	Review
Lossius et al.(110)	1999	Background
Lucki et al.(633)	1986	Excluded – drugs examined not appropriate
Lutz et al.(634)	2005	Excluded – examination of testing method
MacDonald et al.(249)	2000	Background
MacPhee et al.(635)	1986	Excluded via Inclusion/Exclusion criteria
MacPhee et al.(369)	1986	Excluded via Inclusion/Exclusion criteria
Makatsori et al.(636)	2004	Excluded – topic not relevant
Manni et al.(637)	1993	Excluded – topic not relevant
Manni et al.(371)	1993	Excluded – topic not relevant
Marciani et al.(638)	1995	Excluded via Inclusion/Exclusion criteria
Marciani et al.(639)	1999	Background
Marciani et al.(640)	1998	Excluded via Inclusion/Exclusion criteria
Marciani et al.(641)	1992	Excluded via Inclusion/Exclusion criteria
Marks(642)	1982	Background
Martin et al.(643)	2006	Background
Martin et al.(644)	1999	Excluded – topic not relevant
Martin et al.(645)	2001	Excluded – topic not relevant
Matsuura(646)	2000	Background
Mattila et al.(647)	1994	Excluded – examination of testing methodology
Mattson(648)	2004	Excluded via Inclusion/Exclusion criteria
McKee et al.(375)	1994	Excluded via Inclusion/Exclusion criteria
McKee et al.(649)	1992	Excluded – topic not relevant
McKnight and McKnight(178)	1999	Background
Meador(650)	1994	Review
Meador(651)	1998	Review
Meador(196)	2000	Review

Reference	Year	Reason for Exclusion
Meador(652)	2002	Review
Meador(653)	2003	Review
Meador(654)	2006	Review
Meador(655)	1997	Excluded via Inclusion/Exclusion criteria
Meador et al.(194)	2001	Review
Meador et al.(656)	1993	Excluded – topic not relevant
Meador et al.(657)	1991	Excluded – topic not relevant
Meador et al.(658)	1990	Review
Meador et al.(659)	2003	Review
Meador et al.(660)	1995	Excluded – topic not relevant
Meador et al.(661)	1999	Excluded via Inclusion/Exclusion criteria
Meador et al.(662)	2001	Excluded via Inclusion/Exclusion criteria
Meador et al.(663)	2005	Excluded – topic not relevant
Mecarelli et al.(664)	2001	Excluded – topic not relevant
Mecarelli et al.(665)	2004	Excluded – topic not relevant
The RESt-1 Group(666)	2000	Background
Centers for Disease Control and Prevention (CDC)(667)	2005	Background
Michelucci et al.(668)	1992	Excluded via Inclusion/Exclusion criteria
Miller et al.(669)	1999	Background
Moodley et al.(670)	1985	Excluded via Inclusion/Exclusion criteria
Morita(671)	2004	Non-English language
Mortimore et al.(672)	1998	Excluded via Inclusion/Exclusion criteria
Mosher and Rozance(673)	1987	Background
Moskowitz(674)	1984	Background
Mula et al(675)	2003	Excluded via Inclusion/Exclusion criteria
Murthy and Yangala(676)	1999	Background
Nadkarni and Devinsky(677)	2005	Background
Neyens et al.(678)	1995	Excluded via Inclusion/Exclusion criteria
Neyens et al.(679)	1995	Excluded via Inclusion/Exclusion criteria
Ng(680)	1991	Background
Nichols et al.(377)	1993	Review
Norman(219)	1960	Background
O'Brien(681)	1986	Review
O'Donoghue et al.(682)	1998	Excluded – test o f methodology
O'Dougherty et al.(683)	1987	Background
O'Hanlon(684)	1992	Background
Ogunrin et al.(685)	2005	Excluded via Inclusion/Exclusion criteria

Reference	Year	Reason for Exclusion
Ojemann et al.(686)	2001	Excluded via Inclusion/Exclusion criteria
Ooi and Gutrecht(687)	2000	Background
Ortinski and Meador(193)	2004	Review
Ott and Mernoff(688)	1999	Background
Ottman and Lipton(689)	1994	Background
Owczarek et al.(690)	2006	Excluded via Inclusion/Exclusion criteria
Ozkara et al.(691)	2004	Excluded – topic not relevant
Ozuna(692)	1993	Background
Ozuna(693)	1998	Background
Pachlatko(694)	1999	Background
Pacia and Devinsky(695)	1994	Excluded – topic not relevant
Palva and Linnoila(696)	1978	Excluded via Inclusion/Exclusion criteria
Panagopoulos et al.(697)	1997	Excluded via Inclusion/Exclusion criteria
Paradowski and Zagrajek(698)	2005	Background
Parsonage(699)	1970	Background
Parsons(220)	1986	Background
Pellock(700)	2002	Background
Perper(701)	1978	Background
Perucca and Meador(166)	2005	Review
Piazzini et al.(702)	2006	Excluded via Inclusion/Exclusion criteria
Pieters et al.(703)	2003	Excluded via Inclusion/Exclusion criteria
Placidi et al.(704)	2000	Excluded – topic not relevant
Pohlmann-Eden et al.(18)	2006	Background
Popkin and Waller(705)	1989	Background
Prevey et al.(706)	1996	Excluded via Inclusion/Exclusion criteria
Prevey et al.(383)	1996	Excluded via Inclusion//Exclusion criteria
Prevey et al.(707)	1998	Excluded via Inclusion/Exclusion criteria
Prevey et al.(708)	1989	Excluded via Inclusion/Exclusion criteria
Pulliainen and Jokelainen(384)	1994	Excluded via Inclusion/Exclusion criteria
Pulliainen and Jokelainen(709)	1995	Excluded via Inclusion/Exclusion criteria
Quaglieri(710)	1977	Background
Rabasseda(711)	2001	Background
Raffle(712)	1974	Background
Raffle(713)	1981	Background
Rahmann et	2002	Excluded via Inclusion/Exclusion criteria

Reference	Year	Reason for Exclusion
al.(714)		
Rajna et al.(221)	2003	Background
Ramaekers et al.(715)	2002	Excluded – drug not used in US
Ramaratnam et al.(716)	2006	Background
Ramaratnam and Sridharan(717)	2006	Background
Ranganathan and Ramaratnam(718)	2006	Excluded – topic not relevant
Ranheim et al.(719)	1965	Background
Rapeport et al.(720)	1996	Background
Ravi et al.(721)	1995	Excluded via Inclusion/Exclusion criteria
Ray et al.(722)	2002	Background
Ray et al.(723)	1992	Background
Read et al.(385)	1998	Excluded via Inclusion/Exclusion criteria
Reger et al.(190)	2004	Background
Remillard et al.(79)	2002	Background
Reuben(724)	2002	Background
Reynolds and Trimble(725)	1985	Review
Richards(726)	2004	Background
Riddle et al(727)	2004	Excluded via Inclusion/Exclusion criteria
Risdale et al.(728)	2003	Background
Risse(729)	2006	Background
Rizzo et al.(730)	2001	Excluded – topic not relevant
Rogawski and Loscher(731)	2004	Review
Rosche et al.(732)	2004	Excluded via Inclusion/Exclusion criteria
Rostock et al.(733)	1989	Excluded – drug not used in US
Roth et al.(184)	1992	Review
Russ(734)	1995	Excluded – drug not used in US
Ryan et al.(735)	1998	Background
Ryan et al.(736)	1998	Background
Sabers et al.(737)	1995	Review
Sackellares et al.(255)	2006	Excluded – model testing
Saletu et al.(738)	1986	Excluded via Inclusion/Exclusion criteria
Salinsky et al.(739)	2002	Excluded –topic not relevant
Salinsky et al.(740)	1996	Excluded – topic not relevant
Salinsky et al.(741)	2004	Excluded – topic not relevant
Salinsky et al.(742)	2005	Excluded – topic not relevant
Salinsky et al.(743)	1992	Background
Sander(96)	2003	Background
Sander(31)	2006	Background
Sanzenbacher(744)	1977	Background

Reference	Year	Reason for Exclusion
Sasagawa et al.(745)	1989	Background
Schachter(746)	2006	Excluded via Inclusion/Exclusion Criteria
Schain(747)	1982	Background
Schmedding et al.(748)	2004	Background
Schmidt et al.(396)	2000	Review
Schmidt and Wilder(749)	1988	Background
Seigel(750)	1988	Background
Selwa et al.(751)	1994	Excluded via Inclusion/Exclusion criteria
Semah et al.(401)	1994	Excluded via Inclusion/Exclusion criteria
Seneviratne et al.(222)	1998	Background
Seppala et al.(752)	1979	Background
Serafetinides(753)	1975	Background
Sharp(754)	1994	Background
Sheth et al.(84)	2004	Background
Shinnar and Hauser(755)	2002	Background
Shorvon(756)	1995	Background
Sillanpaa and Schmidt(757)	2006	Excluded via Inclusion/Exclusion criteria
Smith(758)	1991	Review
Smith et al.(759)	2006	Background
Smith(760)	2006	Background
Sohn et al.(761)	2002	Excluded via Inclusion/Exclusion criteria
Spencer et al.(276)	2003	Background
Sperling et al.(762)	2002	Excluded – topic for Neurology II report
Spudis et al.(223)	1986	Background
Stables et al.(29)	2002	Background
Stanaway et al.(163)	1983	Background
Stapleton et al.(763)	1986	Background
Starr(764)	2003	Background
Steinwall(765)	1972	Background
Stewart(766)	2005	Review
Stratton(767)	1992	Background
Strauss et al.(768)	1995	Review
Sumer et al.(183)	2005	Background
Sveinbjornsdottir et al.(408)	1994	Excluded via Inclusion/Exclusion criteria
Swann(769)	2001	Review
Takeda et al.(225)	1992	Background
Tassinari and Rubboli(770)	2006	Excluded – topic not relevant
Tata et al.(771)	1994	Excluded via Inclusion/Exclusion criteria

Reference	Year	Reason for Exclusion
Taylor et al.(87)	1996	Background
Taylor et al.(226)	1995	Background
Taylor(772)	1977	Background
Taylor(773)	1988	Background
Temkin(260)	2001	Background
Thomas and Trimble(774)	1996	Exclude – drug not available in the US
Thomas(775)	2000	Background
Thompson et al.(776)	1980	Background
Thompson et al.(777)	1981	Excluded via Inclusion/Exclusion criteria
Thompson(778)	1992	Background
Thompson et al.(779)	2000	Excluded via Inclusion/Exclusion criteria
Thompson and Trimble(780)	1981	Excluded via Inclusion/Exclusion criteria
Thompson and Trimble(781)	1982	Background
Thorbecke(782)	1991	Background
Tiamkao et al.(227)	2006	Background
Tomson et al.(78)	2004	Background
Trimble(783)	1979	Background
Trimble(784)	1981	Background
Trimble(785)	1987	Background
Trimble(786)	1991	Background
Trimble and Thompson(787)	1983	Background
Trimble(788)	1984	Background
Trimble(789)	1987	Excluded – non-English
Troupin et al.(418)	1977	Background
Tuunainen et al.(790)	1995	Excluded via Inclusion/Exclusion
Unsworth(791)	1999	Background
Van der Meyden et al.(792)	1992	Excluded via Inclusion/Exclusion criteria
Van der Meyden and Rodda(793)	2000	Background
Verma et al.(794)	1993	Background
Vermeulen and Aldenkamp(59)	1995	Review
Vining(795)	1987	Excluded via Inclusion/Exclusion criteria
Vorhies(796)	1988	Background
Waller(92)	1965	Background
Walsh(797)	1987	Background
Werz et al.(798)	2006	Excluded – topic not relevant
West(799)	1996	Background
White(800)	2003	Background

Reference	Year	Reason for Exclusion
Whyte and Wroblewski(801)	1989	Excluded via Inclusion/Exclusion criteria
Wick and Zanni(231)	2004	Background
Wiebe et al.(802)	1999	Background
Wilby et al.(422)	2005	Background
Wildin et al.(803)	1993	Excluded – topic not relevant
Willette and Walsh(804)	1983	Background
Withaar et al.(805)	2000	Background
Wong and Lhatoo(806)	2000	Background
Yale et al.(82)	2003	Background
Zaccara et al.(197)	2004	Excluded – topic not relevant
Zaccara et al.(807)	1992	Excluded – topic not relevant

Appendix E: Determining the Stability and Strength of a Body of Evidence

As stated in the main text, ECRI evidence reports differ substantially from other systematic review in that we provide two types of conclusion; qualitative conclusions and quantitative conclusions. In order to reach these conclusions we use an algorithm developed by ECRI to guide the conduct and interpretation of the analyses performed during the development of this evidence report.(57) The algorithm, which is presented in Figure E-3 through Figure E-6, formalizes the process of systematic review by breaking the process down into several discrete steps. At each step, rules are applied that determine the next step in the systematic review process and ultimately to the stability and strength of evidence ratings that are allocated to our conclusions. Because the application of the rules governing each step in the algorithm (henceforth called a decision point) guide the conduct of the systematic review process and how its findings are interpreted, much time and effort was spent in ensuring that the rules and underlying assumptions for each decision point were reasonable.

The algorithm is comprised of three distinct sections: a *General* section, a *Quantitative* section, and a *Qualitative* section. Each of these sections, the decision points that fall within them, and the decision rules that were applied at each step in the present evidence report are described below.

Decision Point 1: Acceptable Quality?

Decision Point 1 serves two purposes: 1) to assess the quality of each included study; 2) to provide a means of excluding studies that are so prone to bias that their reported results cannot be considered useful. To aid in assessing the quality of each of the studies included in this evidence report, we used two study quality assessment instruments. The choice of which instrument to use was based on the design of the study used to address the key questions of interest. In this evidence report we used the ECRI Quality Scale I (for randomized and non-randomized comparative studies), the ECRI Quality Scale III (for pre-post studies) and a revised version of the Newcastle-Ottawa Quality Assessment Scale (for case-control studies).(808) These instruments are presented in Appendix F.

Decision Point 2: Determine Quality of Evidence Base

We classified the overall quality of each key question specific evidence base into one of three distinct categories; high, moderate or low quality. Decisions about the quality of each evidence base were based on data obtained using the quality assessment instruments described above using the criteria presented in Table E-1.

Table E-1. Criteria Used to Categorize Quality of Evidence Base

Category	Median EQS I Score	Median EQS III Score	Median NOQAS Score	Median EQS VI Score
High Quality	≥9.0			
Moderate Quality	6.0 to 8.9	≥9.0	≥8.0	≥8.0
Low Quality	≤6.0	<9.0	<8.0	<8.0

Decision Point 3: Quantitative Analysis Performed?

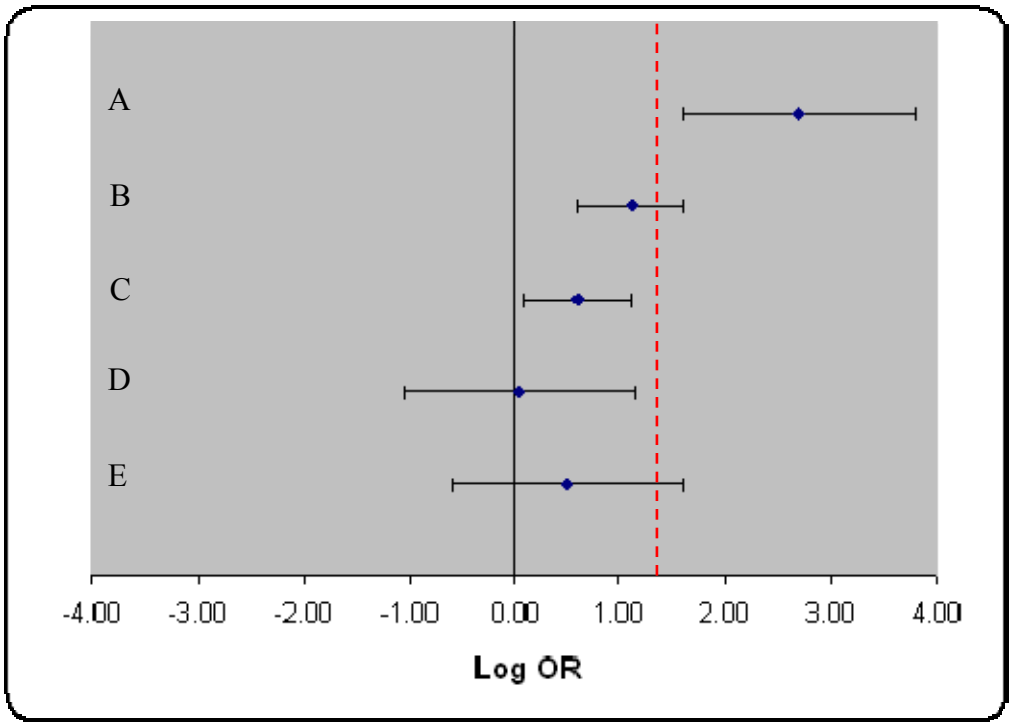
In this evidence report the answer to Decision Point 3 depended on a number of factors; the number of available studies and the adequacy of reporting of study findings. For any given question, combinable data from at least 3 studies must be available before a quantitative analysis will be considered. If 4 or more studies were available but poor reporting precluded ECRI from directly computing relevant effect size estimates for >75% of the available studies, no quantitative analysis were performed. If no quantitative analyses were performed, we moved directly to Decision Point 8 which deals with the assessment of the available evidence with the aim of drawing a purely qualitative conclusion.

Decision Point 4: Are Data Quantitatively Consistent (Homogeneous)?

This decision point was used only when the answer to Decision Point 3 was affirmative and a quantitative analysis was performed. Quantitative consistency refers to the extent to which the quantitative results of different studies are in agreement. The more consistent the evidence, the more precise a summary estimate of treatment effect derived from an evidence base will be. Quantitative consistency refers to consistency tested in a meta-analysis using a test of homogeneity. For this evidence report we used both the Q-statistic and Higgins and Thompson's I^2 statistic.(8) By convention, we considered an evidence base as being quantitatively consistent when I^2 <50% and $P(Q)$ >0.10.

If the findings of the studies included were homogeneous (I^2 <50% and $P(Q)$ >0.10), we obtained a summary effect size estimate by pooling the results of these studies using fixed-effects meta-analysis (FEMA). Having obtained a summary effect size estimate, we then determined whether this estimate effect size estimate was informative. That is, we determined whether the findings of the meta-analysis allowed a conclusion to be drawn. To see what is meant by this, consider Figure E-1. Four of the findings in this figure are informative (A to D). Only finding E is non-informative.

Figure E-1. Informative Findings



Dashed Line = Threshold for a clinically significant difference

Finding A shows that the treatment effect is statistically significant and clinically important. Finding B shows that the treatment effect is statistically significant but it is unclear whether this treatment effect is clinically important. Finding C shows that the treatment effect is statistically significant but that the treatment effect is too small to be considered clinically important. Finding D shows that it is unclear whether there is a statistically important treatment effect, but regardless, this treatment effect is not clinically important. Finding E shows that it is unclear whether there is a statistically important treatment effect and it is also unclear whether the treatment effect is clinically important. This latter finding is thus non-informative.

Decision Point 5: Are Findings Stable (Quantitatively Robust)?

If the findings of the fixed-effects meta-analysis were found to be informative, we next assessed the stability of the summary effect size estimate obtained. Stability refers to the likelihood that a summary effect estimate will be substantially altered by changing the underlying assumptions of the analysis. Analyses that are used to test the stability of an effect size estimate are known as sensitivity analyses. Clearly, ones confidence in the validity of a treatment effect estimate will be greater if sensitivity analyses fail to significantly alter the summary estimate of treatment effect. For this evidence report, we utilized four different sensitivity analyses. These sensitivity analyses are:

1. *Random-effects meta-analysis of complete evidence base.* When the quantitative analysis is performed on a subset of available studies, a random-effects meta-analysis that includes imprecise estimates of treatment effect calculated for all available studies will be performed. For this evidence report, the summary estimate of treatment effect determined

by this analysis will be compared to the summary effect size estimate determined by the original fixed-effects meta-analysis. If the random effects effect size estimate differs from the original fixed-effects meta-analysis by some prespecified tolerance, the original effect size estimate will not be considered stable.

The prespecified tolerance levels for each of the potential effect size estimates we could have utilized in this evidence report are presented in Table E-2.

Table E-2. Prespecified Tolerance Levels

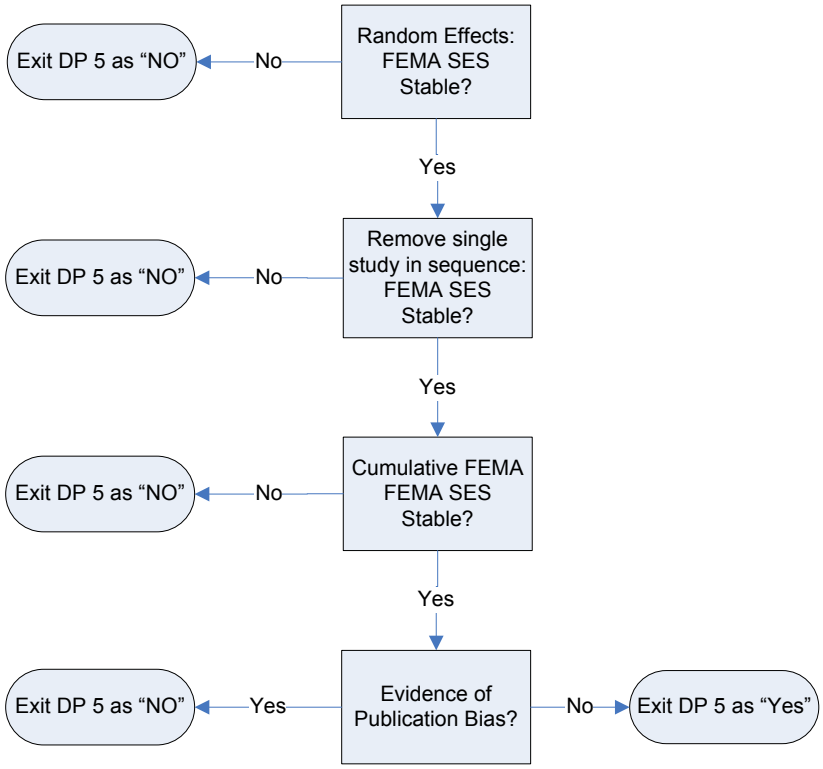
Effect size estimate	WMD	SMD	% of individuals	RR	OR
Tolerance	+/-5%	+/-0.1	+/-5%	+/-0.05	+/-0.05

2. *Removal of one study and repeat meta-analysis.* The purpose of this sensitivity analysis is to determine whether a meta-analysis result is driven by a particular trial. For example, a large trial may have a very strong impact on the results of a meta-analysis because of its high weighting.
3. *Publication bias test.* The publication bias test used in this evidence report was that of Duval and Tweedie.(12-14,73) Based on the degree of asymmetry in a funnel plot constructed from the findings of the included studies, this test(13,14)estimates the number of unpublished studies (and their effect sizes). After addition of any "missing" data to the original meta-analysis, the overall effect size is estimated again. If evidence of publication bias was identified and the summary effect size estimate, adjusted for "missing" studies, differed from the pooled estimate of treatment effect determined by the original fixed-effects meta-analysis by >±5%, the we determined that the findings of our original analysis are not robust and the effect size estimate is not stable.
4. *Cumulative fixed-effects meta-analysis.* Cumulative meta-analysis provides a means by which one can evaluate the effect of the size of the evidence base (in terms of the number of individuals enrolled in the included studies and the number of included studies) on the stability of the calculated effect size estimate. For this evidence report, we performed three different cumulative fixed-effects meta-analyses:
    a. Studies were added in order of weight
    b. Studies were added cumulatively to a fixed-effects meta-analysis by date of publication-oldest study first.
    c. Studies were added cumulatively to a fixed-effects meta-analysis by date-newest study first.

    In each instance, the pooled effect size estimate was considered unstable if any of the last three studies to be added resulted in a change in the cumulative summary effect size estimate effect of >±5%.

Because it is possible to reach Decision Point 6 with two different types of evidence base (100% or <100% ≥75% of total available evidence base), two slightly different sets of sensitivity analyses are needed. Figure E-2 shows the procedural algorithm that were used when dealing with these two types of evidence base.

Figure E-2. Sensitivity Analysis Algorithm 1: Used when Original Fixed-Effects Meta-Analysis Utilized Data from All Available Studies



Decision Points 6 and 7: Exploration of Heterogeneity

We will always attempt to determine the source of heterogeneity when the evidence base consists of 10 or more studies using meta-regression. In preparing this evidence report we did not encounter any situations where we had a heterogeneous evidence base consisting of at least 10 studies. Consequently, Decision Points 6 and 7 are irrelevant to the present report and we do not discuss them further.

Decision Point 8: Are Qualitative Findings Robust?

Decision Point 8 allows one to determine whether the qualitative findings of two or more studies can be overturned by sensitivity analysis. For this evidence report, a single sensitivity analysis was performed–a random-effects cumulative meta-analysis (cREMA). We considered our qualitative findings to be overturned only when the findings of the cREMA altered our qualitative conclusion (i.e., a statistically significant finding became non-significant as studies were added to the evidence base). If the qualitative findings of the last three study additions were in agreement then we concluded that our qualitative findings were robust.

Decision Point 9: Are Data Qualitatively Consistent?

The purpose of this decision point is to determine whether the qualitative findings of an evidence base consisting of only two studies are the same. For example one might ask, "When compared to insulin injection, do all included studies find that inhaled insulin is a significant risk factor for a motor vehicle crash?

Decision Point 10: Is Magnitude of Treatment Effect Large?

When considering the strength of evidence supporting a qualitative conclusion based on only one or two studies, magnitude of effect becomes very important. The more positive the findings, the more confident one can be that new evidence will not overturn ones qualitative conclusion.
The algorithm divides the magnitude of effect into two categories–large and not large.
Determining the threshold above which the observed magnitude of effect can be considered to be "large" cannot usually be determined *a priori*. In cases where it is necessary to make judgments about whether an estimate of treatment effect is extremely large, the project director will present data from the two studies to a committee of three methodologists who will determine whether an effect size estimate is "extremely large" using a modified Delphi technique.

Figure E-3. General Section

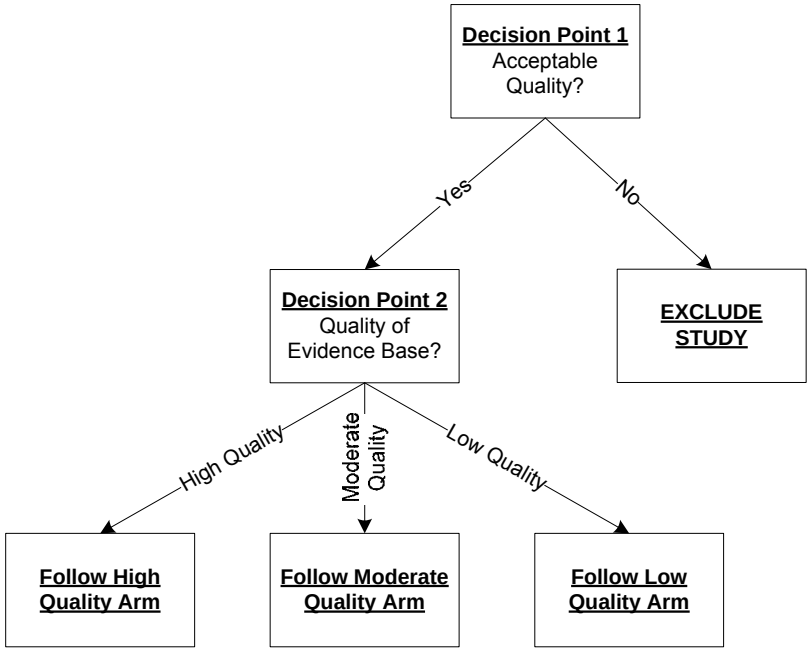


Figure E-4. High Quality Pathway

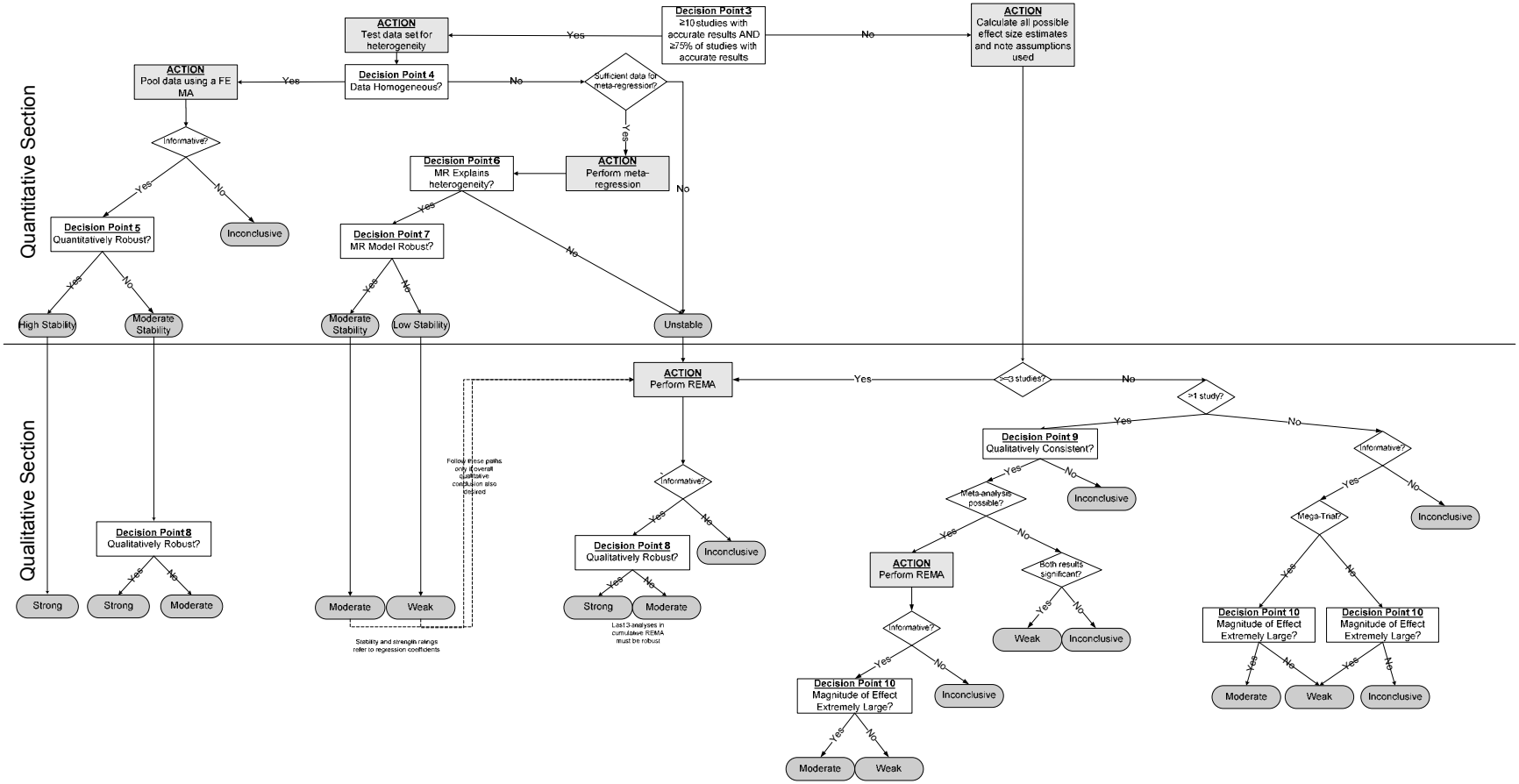


Figure E-5. Moderate Quality Pathway

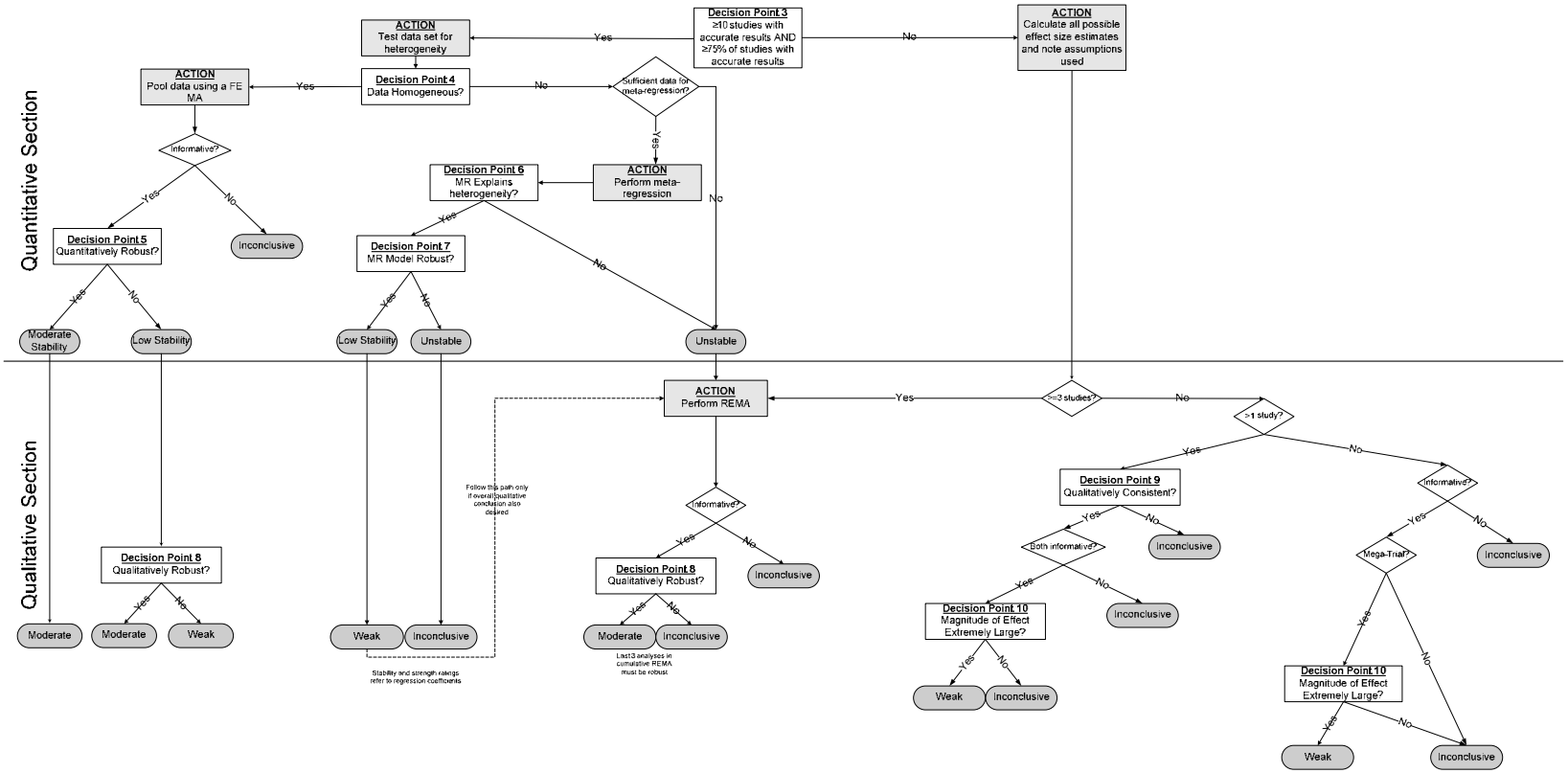
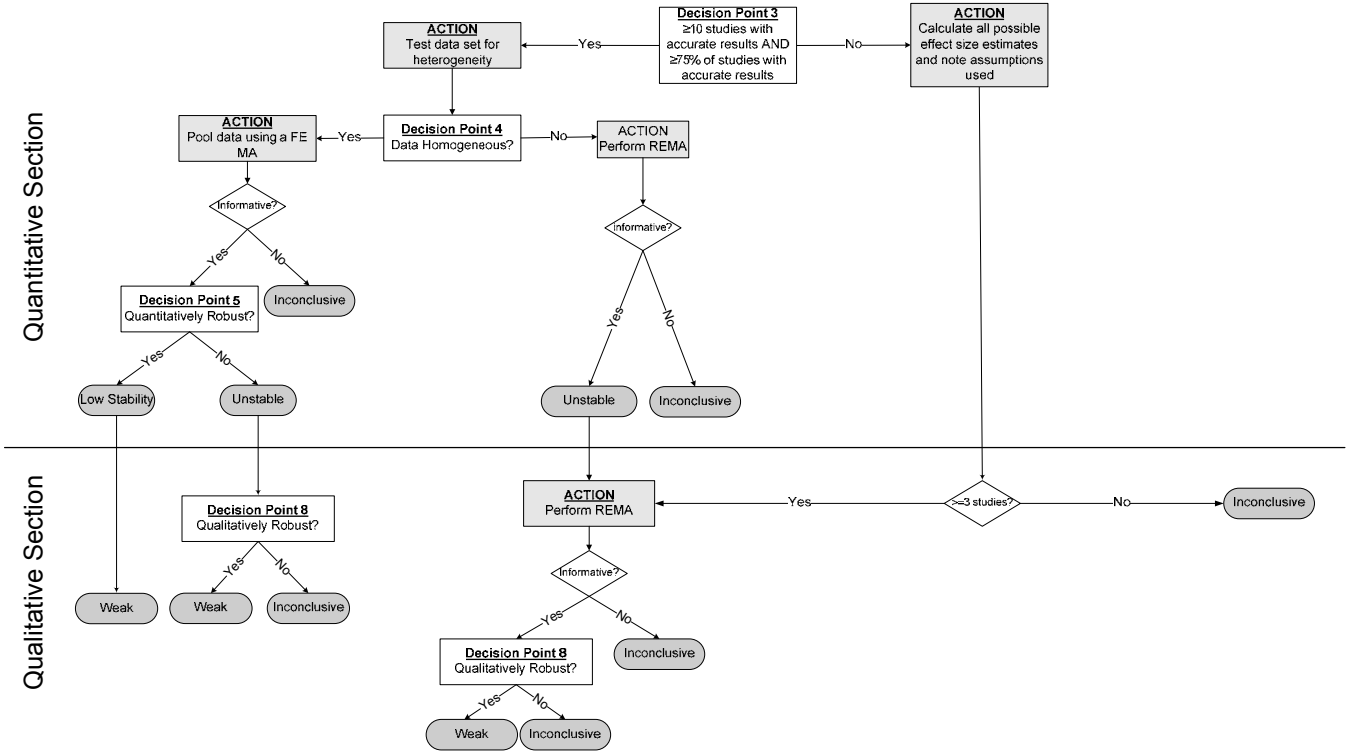


Figure E-6. Low Quality Pathway



Appendix F: Quality Assessment Instruments Used

Three different assessment instruments were used to assess the quality of the studies included in the evidence bases for the key questions addressed in this evidence report; ECRI Quality Scale I for comparative trials, ECRI Quality Checklist X for single arm time-t0-event studies, and a revised version of the Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies.(808)

ECRI Quality Scale I: Controlled Trials

Question #	Question
1	Were patients randomly assigned to the study's groups?
2	Did the study employ stochastic randomization?
3	Were any methods other than randomization used to make the patients in the study's groups comparable?
4	Were patients assigned to groups based on factors other than patient or physician preference?
5	Were the *characteristics* of patients in the different study groups comparable at the time they were assigned to groups?
6	Did patients in the different study groups have similar levels of performance on ALL of the outcome variables at the time they were assigned to groups?
7	Was the comparison of interest prospectively planned
8	Did ≥85% of the patients complete the study?
9	Was there a ≤15% difference in completion rates in the study's groups?
10	Were all of the study's groups concurrently treated?
11	Was compliance with treatment ≥85% in both of the study's groups?
12	Were all of the study's groups treated at the same center?
13	Were subjects blinded to the treatment they received?
14	Did the authors perform any tests after completing the study to ensure that the integrity of the blinding of patients was maintained throughout the study?
15	Was the treating physician blinded to the groups to which the patients were assigned?
16	Were those who assessed the patient's outcomes blinded to the group to which the patients were assigned?
17	Was there concealment of allocation?
18	Was the outcome measure of interest objective **and** was it objectively measured?
19	Were the same laboratory tests, clinical findings, psychological instruments, etc. used to measure the outcomes in all of the study's groups?
20	Was the instrument used to measure the outcome standard?
21	Was the same treatment given to all patients enrolled in the experimental group?
22	Was the same treatment given to all patients enrolled in the control group
23	Were the follow-up times in all of the study's relevant groups approximately equal?
24	Was the funding for this study derived from a source that does not have a financial interest in its results?
25	Were the author's conclusions, as stated in the abstract **or** the article's discussion section supported by the data presented in the articles results section?

ECRI Quality Scale X: Case Series (Time-to-Event)

Question #	Question
1	
2	
3	
4	

5	
6	
7	
8	
9	

Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies

The original Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies consisted of ten questions. We adapted the instrument to better capture some sources of bias that were not considered in the original 10-item scale.

Question #	Question
1	Do the cases have independent validation?
2	Are the cases representative?
3	Are the controls derived from the community?
4	At the designated endpoint of the study, do the controls have the outcome of interest?
5	Does the study control for the most important confounder?
6	Does the study control for any additional confounders?
7	Was exposure/outcome ascertained through a secure record (surgical, etc.)
8	Was the investigator who assessed exposure/outcome blinded to group patient assignment?
9	Was the same method of exposure/outcome ascertainment used for both groups?
10	Was the non-response rate of both groups the same?
11	Was the investigation time of the study the same for both groups?
12	Was the funding free of financial interest?
13	Were the conclusions supported by the data?

Appendix G: Study Summary Tables

Study Summary Tables for Key Question 1

Reference Crancer A, McMurray L. Accident and violation rates of Washington's medically restricted drivers. JAMA 1968;205:74-78														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**	**6**								
	√													
Research Question	Compare driving records of Washington's medically restricted drivers with the driving records of all Washington motorists.													
Study Design	Case-control													
USPSTF Level	II-2													
Population	**Inclusion Criteria**	See Table G-1**.** Washington state licensed drivers. Subjects - drivers with medical licensing restrictions. Medical restriction of interest for this report - epilepsy. This included 1,169 drivers. Medically impaired drivers are brought to the attention of the Department of Motor Vehicles by several means. Information may be offered voluntarily or discovered accidentally. People are reported by the courts, enforcement officers, and concerned citizens, and then required to submit to physical examinations as a condition of retaining a driver's license.												
	Exclusion Criteria	Persons whose condition has not been controlled for six months are refused a license.												
	Study population characteristics	All drivers compared to medically restricted drivers in Washington State. Drivers restricted for epilepsy totaled 1,169.												
	Generalizability to CMV drivers	Unclear												
Procedures	Accident and violation rates for drivers with and without epilepsy license restrictions were compared. Comparisons were done between gender and age groups. The record of each driver and the number of accidents accumulated during the period from Jan. 1961 to Oct. 1, 1967 was determined.													
Statistical Methods	A nonparametric sign test was used to compare age groups of men and women with the corresponding groups in the population. Next, a parametric test making use of the central limit theorem was used to compare the accident rates of the same group to those of the populations. If both approaches agreed in rejecting the null hypothesis at 5% level, a statistical difference was reported. Otherwise, the difference was either higher or lower.													
Quality assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		14	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
		26	**27**	**28**										
Relevant Outcomes Assessed	Accident and violation rates for Epileptic groups compared with driving records of all Washington motorists.													
Results	• See Table G-2**,** Table G-3**, and** Table G-4**.** • Accident rates reported for the epileptic studies were statistically higher for males compared to corresponding population of Washington drivers (54.33 vs. 27.61). • Accident rates for women diagnosed with epilepsy were slightly higher than for the women in the entire Washington driving population, though not statistically higher (19.25 vs. 16.02). • License restrictions for males and females with Epilepsy have statistically higher violation rates compared to corresponding population (110.09 vs. 81.01).													
Authors' Comments	Driving exposure may not be the same in medically restricted license holders compared to the general driving population. Drivers with illness may not report all accidents for fear of losing license or insurance.													
Reviewers' Comments	Drivers might not report medical conditions which could also affect results. Driving exposure not controlled.													

Table G-1. Schedules of medical licensing restrictions

Restriction Category	Drivers Under Each Reexamination Schedule (%)			Total No. of Drivers
	6 Mo	1 Yr	2 Yr	
Diabetes	10	50	40	7,646
Epilepsy	20	50	30	1,169
Heart disease	10	50	40	7,416
Vision deterioration	20	60	20	307
Fainting*	10	50	40	87
Other	10	50	40	4,085
Total	10	50	40	20,710

*"Fainting" category includes drivers with dizzy spells.

Table G-2. A comparison of accident and violation rates: Restricted Groups and Populations

Group With Restrictions	Accidents Per 100*		Violations Per 100*	
	Observed Group	Population†	Observed Group	Population†
License Restrictions				
Diabetes	31.45	26.5	73.33	68.53
Epilepsy	41.4	31.06	110.09	95.56
Fainting	49.42	27.03	98.85	74.15
Heart	25.87	25.28	50.32	56.56
Other	31.75	26.32	79.46	46.21
Vision	25.4	25.48	56.02	57.36
Driving restrictions	32.27	28.72	88.97	87.17

*Average per 100 drivers for the period Jan 1, 1961 to Oct 1, 1967.
†Based on a population with an age distribution comparable to that of each group of drivers with restrictions.

Table G-3. Accident and Violation rates for all Licensed Washington Drivers

Ages (Yr)	Women		Men		Men and Women	
	Total Drivers	Average Per 100*	Total Drivers	Average Per 100*	Total Drivers	Average Per 100*
Accidents						
-17	21,277	6.49	35,381	11.74	56,658	9.76
-20	57,667	14.74	76,813	41.58	134,480	30.92
-25	81,469	18.43	104,173	54.77	185,642	38.82
-30	68,943	14.73	85,971	43.02	154,914	30.42
-35	66,224	14.71	78,611	37.89	144,835	27.29
-50	220,754	16.44	261,136	34.08	481,890	26
-65	141,418	16.19	201,711	32.68	343,129	25.53
& older	40,753	16.66	88,885	28	129,638	24.44
Total	698,505	16.02	932,681	36.29	1,631,186	27.61
Violations						
-17	21,277	5.46	35,381	30.19	56,658	21.31
-20	57,667	27.55	76,813	142.35	134,480	92.97
-25	81,469	46.27	104,173	241.66	185,642	155.91
-30	68,943	37.82	85,971	173.12	154,914	112.9
-35	66,224	34.69	78,611	130.09	144,835	86.47
-50	220,754	35.48	261,136	99.16	481,890	69.98
-65	141,418	31.77	201,711	75.42	343,129	57.43
& older	40,753	30.41	88,885	54.12	129,638	46.66
Total	698,505	34.31	932,681	115.99	1,631,186	81.01

*Average per 100 drivers for the period Jan 1, 1961 to Oct 1, 1967.

Table G-4. Accident and Violation Rates for drivers with an Epilepsy License Restriction

Age (Yr)	Women		Men		Men and Women	
	Total Drivers	Average Per 100*	Total Drivers	Average Per 100*	Total Drivers	Average Per 100*
Accidents						
13-17	24	. . .	48	12.5	72	8.33
18-20	60	20	122	53.28	182	42.31
21-25	98	18.37	171	78.95	269	56.88
26-30	51	17.65	89	66.29	140	48.57
31-35	51	19.6	76	40.78	127	32.28
36-50	99	30.3	149	44.29	248	34.67
51-65	38	34.21	63	49.2	101	43.56
66 & older	10	10	20	40	30	30
Total	431	19.25	738	54.33	1,169	41.40
Violations						
13-17	24	8.33	48	16.67	72	13.89
18-20	60	28.33	122	126.23	182	93.96
21-25	98	56.73	171	270.76	269	185.5
26-30	51	37.25	89	191.01	140	135
31-35	51	37.25	76	140.78	127	99.21
36-50	99	32.32	149	124.83	248	87.9
51-65	38	36.84	63	77.77	101	62.37
66 & older	10	20	20	45	30	36.66
Total	431	32.71	738	156.28	1,169	110.99

*Average per 100 drivers for the period Jan 1, 1961 to Oct 1, 1967.

<table>
<tr><td colspan="9">Davis TG, Wehling EH., Carpenter RL. Oklahoma's Medically Restricted Drivers. A Study Of Selected Medical Conditions. Oklahoma State Medical Association Journal July 1973:66: 322-327</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td>5</td><td>6</td></tr>
<tr><td>√</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="9">Comparison of medical and driving records of individuals with chronic conditions reported to the Oklahoma Department of Public Safety with the driving records of individuals not known to have chronic medical conditions.</td></tr>
<tr><td>Study Design</td><td colspan="9">Matched Case-control study</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="8">Individuals suffering from diabetes, cardiac or circulatory conditions, epilepsy, or neurological disorders such as a stroke or chronic brain syndrome (Chronic Disease Group) with driving license granted after review by the Oklahoma Department of Public Safety in 1969.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="8">Medically restricted drivers whose licenses were revoked or suspended for all or part of 1970.</td></tr>
<tr><td>Study population characteristics</td><td colspan="8">Chronic Disease Group: N= 318 (Epilepsy N = 77)
Male: 69.8%
>65 years of age: 20%,
≤ 24 years of age: 43%
25-64 years of age: 37%.
Epilepsy and other neurological conditions were more common in the 25-64 age groups.
Control Group: N = 1,651,245
Male: 54.2
Age: NR</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="8">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="9">The driving records of all individuals restricted drivers, who were granted drivers licenses after being reviewed by the Oklahoma Medical Advisory Committee (OMAC) in 1969 were studied. The number of crashes and moving violations accumulated during 1970 was recorded in individual cards. The crash rates were compared with matched age and sex crash rates of all of Oklahoma's 1, 651,245 licensed drivers for the year 1970. Accidents were considered to be single or multiple motor vehicle crash in which the subject was the driver of a motor vehicle. Speeding, exceeding the legal or safe speed limits, and other moving violations defined by the Department of Public Safety were recorded under the heading of moving violations. .All crash In which the medically restricted person was a driver were included in the study. Only moving violations for which the medically restricted driver entered a plea of guilty, was convicted by a court, paid a fine or offered bond forfeiture were included in the study.</td></tr>
<tr><td>Statistical Methods</td><td colspan="9">Crash and violation rates compared</td></tr>
<tr><td rowspan="5">Quality assessment</td><td rowspan="2">Quality score = 9.0</td><td colspan="13">Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td rowspan="3">Moderate</td><td>S</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td></tr>
<tr><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>26</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="9">Frequency of motor vehicle crashes</td></tr>
<tr><td>Results</td><td colspan="9">See Table G-7and Table G-8. For epileptic drivers, it was determined that males as a group had an crash rate approximately three times greater that of all licensed males. The crash rate of each group for which a rate could be calculated was also higher that the matched age groups of the population. As might be expected, the 17-21 and 22-24 age groups were responsible for the highest rates. The violation rate was considerably higher that the overall population violation rate. Again, the 17-21 and 22-24 age groups were responsible for these highest rates.
Epileptic females as a group had a higher crash rate than that of all licensed females and had a lower violation rate than the overall population. The 17-2 age group accounted for all the violations attributed to female epileptics.
The crude and overall violation rate for all licensed Oklahoma drivers was determined to be 26.4 per 100 drivers. The total number of moving violations reported by the Department of Public Safety was 486,129.
Speeding was the most common violation attributed to epileptics and persons in the other neurological category.</td></tr>
<tr><td>Authors' Comments</td><td colspan="9">Oklahoma drivers diagnosed as being epileptic, diabetic or having other neurological conditions have higher crash and violation rates than licensed Oklahoma drivers not known to be affected.</td></tr>
</table>

Table G-5. Distribution for Violations for Selected Chronic Diseases

Number of Violations	Diabetes		Cardiac and Circulatory		Epilepsy		Other Neurological	
	N	Per cent	N	Per cent	N	Per cent	N	Per cent
0	79	73.15	47	85.45	57	74.03	60	76.92
1	24	22.22	5	9.09	13	16.88	9	11.54
2	0	0.00	2	3.64	5	6.49	6	7.69
3	4	3.70	1	1.82	1	1.30	0	0.00
4+	1	0.93	0	0.00	1	1.30	3	3.85
Totals	108		55		77		78	

Table G-6. Distribution for Accidents for Selected Chronic Diseases

Number of Violations	Diabetes		Cardiac and Circulatory		Epilepsy		Other Neurological	
	N	Per cent	N	Per cent	N	Per cent	N	Per cent
0	101	93.52	50	90.91	65	84.41	68	87.18
1	6	5.56	5	9.09	10	12.98	8	10.25
2	1	0.92	0	0.00	2	2.61	2	2.57
3+	0	0.00	0	0.00	0	0.00	0	0.00
Totals	108		55		77		78	

Table G-7. Moving Violation Rates for Selected Conditions in Medically Handicapped Oklahoma Drivers, 1970

	Male	Female	Male & Female
Diabetes	49.2	20.9	38.0
Cardiac & Circulatory	24.4	14.3	21.8
Epilepsy	49.0	19.3	39.0
Other Neurological	50.8	15.4	42.3
All Licensed Oklahoma Drivers			26.4

*Violations per 100 drivers

Table G-8. Accident Rates for Selected Conditions in Medically Handicapped Oklahoma Drivers, 1970

	Male	Female	Male & Female
Diabetes	9.2	4.7	7.4
Cardiac & Circulatory	12.2	0.0	9.1
Epilepsy	23.5	7.7	18.2
Other Neurological	10.8	30.8	14.1
All Licensed Oklahoma Drivers	8.7	4.8	7.1

*Accidents per 100 drivers

<table>
<tr><td colspan="15">Hansiota P. and Broste S.K. Epilepsy and traffic safety. Epilepsia 1993; 34(5): 852-858</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="3">6</td></tr>
<tr><td>√</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="3"></td></tr>
<tr><td>Research Question</td><td colspan="14">1. To compare crashes and violation rates of licensed drivers with epilepsy with those of all drivers without epilepsy from the same area.
2. To identify medical and other factors contributing to the higher age-adjusted rates of traffic crashes and moving violations among drivers with epilepsy.</td></tr>
<tr><td>Study Design</td><td colspan="14">Case-control study</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Licensed drivers with epilepsy identified in a seven ZIP postal code area served almost exclusively by the Marschfield Clinic (WI, USA) and licensed drivers without epilepsy from the same area.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">N = 241 epilepsy patients with driver's licenses
See Table G-9 for complete details.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">The medical records of 241 drivers with epilepsy were studied. Comparison of crash and violation rates of licensed drivers with epilepsy with those of all drivers without epilepsy was made. Information abstracted from medical charts was used to identify potential risk factors for traffic crashes and violations among the drivers. The data collected included date of the first seizure, type of seizure recorded, and presence of abnormal EEGs; we also determined where there was a history of only one seizure. Aspects of the medical history during *the 4-year study period (1985-1988)* was also recorded, including the antiepileptic drugs (AEDs) administered, history of noncompliance, severe AED reactions and coexisting medical conditions; we also ascertained whether the physician and recommended that the patient not drive. Also recorded were the counts of number of seizures recorded in the 2 years preceding the study period as well as during the study period itself. Data on age, sex, and marital status were also used. For each subject with a license during any part of the study period, *the number of crashes and violations and the number of years of exposure was obtained* from a data tape supplied by the Wisconsin Department of Transportation. No information was available regarding whether accidents or violations occurred as a direct result of a seizure.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">*For comparison of crash and violation rates* of licensed drivers with epilepsy with those of all drivers without epilepsy, indirect age standardization was used. As a summary measure, the standardized mishap ratio (SMR) was computed for each type of accident and violation. The 95% confidence interval (CI) for the standardized mishap ratio was constructed by approximate method as described by Rothman and Boice (1979). The significance (p-value) of the difference between the standardized mishap ratio and 1 was based on the probability in the two tails of the Poisson distribution that the deviation from the expected number of mishaps was as large or larger than that observed, in either direction.
To evaluate the association between patient medical and demographic characteristics, and the risk of crashes and violations, we used two approaches. The first approach involved separation of the data sets according to the exposure of interest. The age-adjusted relative risk of the type of mishap of interest for affected vs. nonaffected drivers was calculated by the Mantel-Haenszel estimate for cohort data. Approximate 95% CIs and p-values for the relative risk were calculated by a variance formula of Breslow.
A second approach involved use of Poisson regression methods to adjust simultaneously for multiple covariates. No attempt was made to adjust for multiple-hypothesis testing; as a result, the observed associations should be considered suggestive. Parameter estimates and associated SE were used to calculate estimates and 95% CIs for the relative risk.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Quality Score = 7.8</td><td colspan="13">Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td></td><td>S</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="4">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>26</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1) Comparison of crashes and violation rates of licensed drivers with epilepsy with those of all other licensed drivers in the area.
2) Association between patient medical and demographic characteristics, and the risk of crashes and violations,</td></tr>
<tr><td>Results</td><td colspan="14">(Table G-10 and Table G-11) Comparison of accident and violation rates of licensed drivers with epilepsy with those of all other licensed drivers in the area.
During the 4-year study period, patients with epilepsy had 54 traffic crashes and 82 moving violations. Property damage crashes were more numerous than crashes involving injury.
The standardized mishap ratios (SMR) shown are the results of indirect age standardization, and ratios > 1 indicate higher risk among patients with epilepsy. SMR for licensed drivers with epilepsy (any crash): 1.33 (95% CI 1.00- 1.73)
Epileptic drivers with driver's licenses had a significantly increased risk for careless driving, alcohol or drug violations, injury crashes, and all accidents combined as compared to the general population. Speeding violation (the most frequent violation) occurred at a lower</td></tr>
</table>

	rate among patients with epilepsy. **(Table G-12, Table G-13, and Table G-14) Association between patient medical and demographic characteristics, and the risk of accidents and violations.** Young age, unmarried state, history of multiple seizures, and lack of antiepileptic drug (AED) treatment appear to be risk factors for crashes among drivers who had a history of seizures. Male sex, psychiatric disorders, alcohol abuse, and generalized seizures or complex partial seizures (CPS) were also suggestively associated with higher risk. For moving violations, young age, male sex, unmarried state, symptomatic etiology, and history of alcohol abuse contributed to increased risk. EEG abnormalities, specific or nonspecific, seizure frequency, and age of onset had no significant association with traffic risk in this study.
Authors' Comments	This study suggest that as group patients with controlled seizures (as defined by the seizure-free interval required to obtain a driver's licenses) pose a somewhat higher risk for violations and crashes than does the general public. Drivers with epilepsy appear to have identifiable factors for traffic mishaps, especially crashes.

Table G-9. Characteristics of Epilepsy Patients with and without regular driver's licenses

Variable	Patients with licenses		Patients without licenses	
	n	Observed statistic	n	Observed statistic
Male (%)	241	57.7	191	42.4
Mean age (yr)	241	43.4	191	46.2
Currently married (%)	216	70.8	179	35.2
Mean years since first seizure	241	14.8	187	18.7
History of single seizure (%)	239	21.6	186	16.7
Abnormal EEG (%)	237	65.8	190	80.5
History (1985–1988) with (%)				
⩾1 seizures	231	44.2	169	47.3
No AEDs	229	17.5	159	9.4
Noncompliance with treatment	227	18.9	154	15.6
Stroke, CVA, or TIA	228	14.9	153	21.6
Mental retardation	228	1.8	164	40.9
Dementia or Alzheimer's disease	228	6.1	155	17.4
Clinical depression	228	8.3	153	4.6
Psychiatric illness	229	10.9	162	21.6
Alcohol or drug abuse	229	7.4	155	6.5

AEDs, antiepileptic drugs; CVA, cerebrovascular accident; TIA, transient ischemic attack.

Table G-10. Number of Accidents and Violations (1985 to 1988) Among Licensed Drivers with Epilepsy

Frequency	Injury accidents		Property damage accidents		Any accident		Careless driving violations		Speeding violations		Alcohol or drug violations		Any moving violation	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0	225	93.4	211	87.6	199	82.6	219	90.9	209	86.7	231	95.9	186	77.2
1	15	6.2	23	9.5	32	13.3	17	7.1	25	10.4	8	3.3	39	16.2
2	1	0.4	7	2.9	9	3.7	4	1.7	7	2.9	0	0.0	9	3.7
3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.8	5	2.1
4	0	0.0	0	0.0	1	0.4	1	0.4	0	0.0	0	0.0	1	0.4
5	0	0	0	0	0	0	0	0.0	0	0.0	0	0.0	0	0.0
6	0	0	0	0	0	0	0	0.0	0	0.0	0	0.0	1	0.4

Table G-11. SMR for Licensed Drivers with Epilepsy by Type of Mishap

Mishap type	SMR	95% CI[a]
Careless driving violations	1.57[b]	1.05–2.25
Speeding violations	0.80	0.57–1.09
Alcohol or drug violations	2.75[c]	1.50–4.62
Any moving violation	1.13	0.90–1.41
Injury accidents	1.63[b]	0.95–2.60
Property damage accidents	1.23	0.86–1.69
Any accident	1.33[b]	1.00–1.73

SMR, standardized mishap ratio.
[a] 95% confidence interval for the SMR.
[b] $p < 0.05$ for comparison of SMR with 1.00.
[c] $p < 0.01$ for comparison of SMR with 1.00.

Table G-12. Rates of Accidents and Violations Among Licensed Drivers with Epilepsy by Age

Age	Person-years	Accidents		Moving violations	
		n	Rate[a]	n	Rate[a]
<25	179.2	26	145.1	29	161.8
25–34	176.7	10	56.6	23	130.2
35–44	144.2	6	41.6	15	104.0
45–54	70.4	4	56.8	7	99.5
55–64	82.7	1	12.1	6	72.6
≥65	163.7	7	42.8	2	12.2
Total	817.0	54	66.1	82	100.4

[a] Rate per 1,000 person-years.

Table G-13. Estimates of Effect of Patient Characteristics on Risk of Accidents

Patient characteristic	Age adjusted		Poisson model	
	RR[a]	95% CI[b]	RR[c]	95% CI[b]
Male sex[d]	1.82[e]	1.02–3.24	1.52	0.83–2.80
Married[f,g]	0.34[g]	0.21–0.56	0.34[g]	0.17–0.65
Receiving AEDs	0.75	0.40–1.41	0.41[g]	0.21–0.79
History of single seizure	0.44	0.16–1.23	0.39[e]	0.15–1.00
History of psychiatric disorder	2.25[g]	1.66–3.04	2.11	0.93–4.76
History of alcohol abuse[e]	3.43[g]	2.52–4.67	1.90	0.79–4.58
History of noncompliance	1.28	0.68–2.40	0.85	0.39–1.85
Symptomatic versus idiopathic etiology	1.06	0.57–1.96	1.49	0.63–3.52
History of severe reaction to prescribed medication	1.25[e]	1.03–1.52	1.23	0.40–3.72
Epileptic seizure during study period	0.82	0.54–1.26	0.82	0.40–1.66
More than 10 years since first seizure	1.30	0.74–2.26	1.19	0.61–2.34
Specific versus non-specific EEG abnormalities	0.86	0.45–1.63	1.01	0.43–2.38
Types of seizures experienced				
Simple	—	—	1.13	0.13–10.00
Complex partial	—	—	2.67	0.94–7.60
Generalized	—	—	1.79	0.81–3.98

AEDs, antiepileptic drugs; RR, relative risk.
[a] Estimated relative risk with characteristic versus without, adjusted for age by Mantel-Haenszel methods.
[b] 95% Confidence interval for relative risk.
[c] Estimated relative risk based on Poisson regression model. Relative risks assume no interactions involving that characteristic. The model is described in the Methods section.
[d] Interaction of sex and marital status suggests markedly lower risk for married females.
[e] $p < 0.05$ for comparison of RR with 1.00.
[f] Interaction of marital status and alcohol abuse suggests that increased risk due to alcohol abuse is primarily among married patients.
[g] $p < 0.01$ for comparison of RR with 1.00.

Table G-14. Estimates of Effects of Patient Characteristics on Risk of Moving Violations

Patient characteristic	Age adjusted		Poisson model	
	RR[a]	95% CI[b]	RR[c]	95% CI[b]
Male sex	3.60[d]	2.14–6.05	3.48[d]	1.96–6.18
Married	0.39[d]	0.25–0.61	0.49[d]	0.29–0.84
Receiving AEDs	1.31	0.70–2.47	1.20	0.64–2.24
History of single seizure	0.78	0.43–1.40	0.86	0.47–1.57
History of psychiatric disorder	1.77[d]	1.38–2.26	1.42	0.73–2.77
History of alcohol abuse	4.41[d]	3.16–6.17	2.64[d]	1.40–4.99
History of noncompliance	1.48	0.86–2.56	1.17	0.69–1.66
Symptomatic versus idiopathic etiology	1.94[e]	1.14–3.31	2.01[d]	1.29–3.14
History of severe reaction to prescribed medication	2.13[d]	1.76–2.58	1.87	0.84–4.17
Epileptic seizure during study period	1.37	0.93–2.00	1.17	0.71–1.92
More than 10 years since first seizure	1.17	0.81–1.70	1.08	0.66–1.76
Specific versus nonspecific EEG abnormalities	0.71	0.41–1.24	1.06	0.52–2.16
Types of seizures experienced				
Simple	—	—	1.54	0.42–5.60
Complex partial	—	—	0.74	0.25–2.18
Generalized	—	—	0.82	0.48–1.40

Abbreviations as in Table 6.
[a] Estimated relative risk with characteristic versus without, adjusted for age by Mantel-Haenszel methods.
[b] 95% Confidence interval for relative risk.
[c] Estimated relative risk based on Poisson regression model. Relative risks assume no interactions involving that characteristic. Model is described in Methods section.
[d] $p < 0.01$ for comparison of RR with 1.00.
[e] $p < 0.05$ for comparison of RR with 1.00.

<table>
<tr><td colspan="9">Lings S. Increased driving accidents frequency in Danish patients with epilepsy. Neurology 2001;57: 435-439</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td>5</td><td>6</td></tr>
<tr><td>√</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="9">To determine whether drivers who have epilepsy are at greater risk of being involved in traffic crashes.</td></tr>
<tr><td>Study Design</td><td colspan="9">Matched Case-control study</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="8">Drivers with epilepsy as main or additional diagnosis drawn from the patient register at Odense University Hospital, Denmark. The controls were drawn from the Central Person Registry and consisted of individuals matched for age, gender, place of residence, and exposure period.
All had nonprofessional driver's licenses without restrictions</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="8">1) Persons who had not had a license during the study period.
2) Drivers with a professional license (two from the control group only) because they are exposed to special risks.
3) Persons with recorded diagnoses of other neurological diseases, cerebrovascular disease, diabetes, psychoses, dementia, seizures, alcoholism, drug dependence or poisoning of any kind.</td></tr>
<tr><td>Study population characteristics</td><td colspan="8"><table><tr><td></td><td><u>Epilepsy group</u></td><td><u>Control Group</u></td></tr><tr><td>n</td><td>159</td><td>559</td></tr><tr><td>Sex:</td><td></td><td></td></tr><tr><td>Male, no.(%)</td><td>87 (54.7)</td><td>342 (61.2)</td></tr><tr><td>Female, .no.(%)</td><td>72 (45.3)</td><td>217 (38.8)</td></tr><tr><td>Age: (yrs) Median</td><td></td><td></td></tr><tr><td>Male</td><td>38.8</td><td>38.1</td></tr><tr><td>Female</td><td>35.9</td><td>35.0</td></tr><tr><td>Age: (yrs) Range</td><td></td><td></td></tr><tr><td>Male</td><td>18.9 – 78.5</td><td>18.2 – 79.0</td></tr><tr><td>Female</td><td>20.7 – 69.9</td><td>20.3 – 69.0</td></tr></table></td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="8">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="9">A 10-year historical cohort register study was carried out. Patients were drawn from the patient register at Odense University Hospital, Denmark, from January 1,1980 to December 31, 1989 and comprised patients under the diagnosis epilepsia 345 (International Classification of Disease [ICD], eight revision) as main or additional diagnosis. The controls were drawn from the Central Person Registry. The number of controls for each epilepsy patient varied between one and seven, the median being four. The relevant exposure period, "T rel ", was defined as the period of time after the date of diagnosis during which the member held a driving license. Road traffic accident information was drawn from the Accident Analysis Group's Register (AAG) at the Odense University Hospital.</td></tr>
<tr><td>Statistical Methods</td><td colspan="9">Crash rates per 1,000 person-years were calculated for both groups by the use of "T rel" and information about accidents in that period. Confidence intervals and p values for the rate ratio are based on exact inference procedures provided by the 'iri' command of STATA.</td></tr>
<tr><td rowspan="5">Quality assessment</td><td rowspan="2">Quality Score = 8.46</td><td colspan="8">Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td></td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="4">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>26</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="9">The outcome measure was treatment at the casualty department after a motor vehicle crash as a car driver. Crash frequency was calculated based on the number of years a driving license had been held and not in relation to actual driving distance (mileage)</td></tr>
<tr><td>Results</td><td colspan="9">Over the period of 1980 to 1989, ten patients with epilepsy and five controls were treated at the casualty department.
"T rel "varied for both group between 0.02 and 10 years, The median in both group was 7.56 years.
The total "T rel" (sum of cases) in the epilepsy group, was 1,063.72 years and 3,727.44 years in the control group.
Thus, the crash rate per 1,000 person-years in the epilepsy group was (10/1,063.72)*1,000 = 9.4, in the control group (5/3,727.44)* 1,000 = 1.34. The ratio between those values was 9.4/1.34 = 7.01 (CI 2.18 to 26.13, p = 0.0003) indicating that the crash rate was distinctly (seven times) higher in the epilepsy group, than in the control group.
-In the epilepsy group, there were four collisions between vehicles, four collisions with fixed objects, and two cases without counterpart (one overturning and one driving into an excavation).
- In the control group, there were three collisions between vehicles and two collisions with fixed objects in the control group.</td></tr>
</table>

	- An Injury Severity Score was calculated on the basis of the Abbreviated injury Scale (< 7 = minor injury, 7 to 12 = moderate injury, >12 = serious injury) In the epilepsy group: 9 injuries were classified as minor and one as serious. In the control group, all five were minor. In view of the small number involved, no further statistical analysis was performed.
Authors' Comments	Drivers with epilepsy are more likely than controls to be treated at a casualty department after having a motor vehicle crash. The author noted that the outcome measure, driver's treatment at the emergency department after a crash, must be considered as insensitive because such events are rare, and the small sample numbers is a patent weakness. Furthermore, this method does not take into account minor crashes or injuries leading to a visit, not by the driver himself but by other road users or passengers, nor does it take into account crashes that only involve material damage. The author concluded that the seven-fold magnitude of risk was surprising. The differences in findings with previous studies may be explained by better data quality in the current investigation because of access to register data, including hospital data rather than the participants' own information or insurance files. The author also noted that previous studies had not adequately excluded participants with other neurologic diseases or addictions. However, due to the small sample size, drastic consequences regarding regulations should be avoided until these results have been substantiated by further investigations.

Reference: Sheth SG, Krauss G, Krumholz A, Li G. Mortality in epilepsy: Driving fatalities vs other causes of death in patients with epilepsy. Neurology 2004; 63: 1002-1007.														
Key Questions Addressed	1	2	3	4	5	6								
	√													
Research Question	Are individuals diagnosed with epilepsy at a greater risk for serious crashes and injury than the general driving population?													
Study Design	Prospective Cohort													
Population	**Inclusion Criteria**	Subjects are seizure-free for 3-12 months before driving or elect to individualize restrictions based on limited risk data.												
	Exclusion Criteria	NR												
	Study population Characteristics	The demographics for patients with seizures, other medical conditions, and no associated medical conditions who died in motor vehicle crashes were varied. (Table G-15)												
	Generalizability to CMV drivers	Unclear												
Methods	• Multiple causes of mortality data files for years 1995-1997 analyzed using US death certificates provided by NCHS (National Center for Health Statistics). • ICD-9 codes 345.0 to 345.9, 780.3 used to screen for Epilepsy. • Crash rates for Epilepsy calculated by comparing the number of fatal crashes associated with disorder with its annual prevalence. • Disease-specific fatal crash rates compared to alcohol-related fatal crashes. • Prevalence estimates calculated for epileptic crash rates of 5.1/1,000 • State driving restrictions for patients with seizures classified into 4 categories: seizure free requirement minimums of 3, 6, or 12 months and fourth group states that individualize driving restrictions. • Adjustments made for age and population size of each state.													
Statistical Methods	• PMR- proportionate mortality ratio for fatal crashes and other causes of death was determined for individuals diagnosed with epilepsy or convulsions. PMR for fatal crashes is the proportion of patients with epilepsy or convulsion who died each year in seizure-related motor vehicle crash compared to expected ratios from the general population. • Whisker-box plots for rates of fatal crashes according to months of seizure free intervals required by driving laws in different states in the U.S.													
Quality assessment	Study quality	1	2	3	4	5	6	7	8	9	10	11	12	13
	Moderate	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Risk of crashes posed by patients with seizures and seizure-related motor vehicle fatalities.													
Results	• Rates for fatal seizure-related crashes among patients with epilepsy (8.6 per 100,000) were lower than the rates for fatal crashes in the general population (22.4 per 100,000), and small compared to driver fatalities associated with alcohol abuse and alcoholism (72.4 per 100,000 per year, range 68.65 to 75.54) and young drivers (16-24 years) 28.08 per 100,000). • Fatal crash rates for the general population were 2.6 times greater than those for patients with seizures, and patients with associated alcohol abuse had fatal crash rates eight times greater than those for patients with seizures. • See Table G-16 and Table G-17.													
Authors' Comments	• Fatal driver crashes due to seizures are uncommon. Finding support current public policy—permitting patients whose seizures are controlled to drive. • Would be useful to extend findings of crash risks for individuals diagnosed with epilepsy, to include detailed information on number of drivers and miles driven to determine whether individual patients should drive.													
Reviewers' Comments	Study population and characteristics unclear													

Table G-15. Demographics for all deaths due to motor vehicle accidents in the United States (1995-1997)

	Medical causes associated with fatal crashes (mean values: 1995–97)			
Characteristics	Epilepsy	Cardiovascular	Diabetes	Total accidents
Male	63 (73.3)	1,220 (68.7)	84 (58.3)	29,396 (66.8)
Female	23 (26.7)	580 (31.3)	60 (41.7)	14,631 (33.2)
Marital status				
Single	35 (40.7)	372 (20.7)	15 (10.4)	18,508 (42.0)
Married	27 (31.4)	817 (45.4)	75 (52.1)	15,796 (35.9)
Widowed	8 (9.3)	386 (21.4)	32 (22.2)	3,893 (8.7)
Divorced	16 (18.6)	219 (12.2)	21 (14.6)	5,625 (12.8)
Not stated	0	6 (0.3)	1 (0.7)	268 (0.6)
Age groups, y				
15–19	4	92	2	5,301
20–24	6	82	1	5,279
25–29	9	68	2	4,103
30–34	7	64	2	3,762
35–39	10	65	5	3,640
40–44	10	75	7	3,107
45–49	7	82	9	2,592
50–54	5	85	11	2,043
55–59	5	110	10	1,687
60–64	4	116	18	1,572
65–69	5	143	20	1,619
70–74	4	174	19	1,793
75–79	3	212	19	1,794
80–84	3	197	13	1,506
85–89	1	126	6	888
90–94	1	39	1	258
95–99	0	8	0	36
100–104	0	1	0	3

Table G-16. Disease Specific Rates of Fatal Crashes in the United States (1995 to 1997)

Medical causes of fatal crashes	Prevalence* rates (1995–97)	Estimated prevalence of the disease in US (1995–97)	Disease-specific rates of fatal crashes (per 100,000 pop)
Seizures	5.1	1,000,585	8.8
Diabetes mellitus	39.1	7,670,768	1.88
Cardiovascular and hypertensive disorders	245.2	48,104,153	3.74
Alcohol abuse and alcoholism	94.6	18,558,943	72.4
Young drivers (<25 years)		37,670,000	28.08
Total population		196,183,333	22.44

* Prevalence of that medical condition in US population (per 1,000 persons above 18 years of age).

Table G-17. Different underlying causes of death in patients with seizures and their proportionate mortality as compared with total population

Medical conditions	ICD-9 codes	Underlying cause of deaths (mean) (1995–97)		Proportionate mortality ratio	95% CI PMR
		In total population (n = 2,317,016)	In epilepsy patients (n = 22,194)		
Epilepsy	345	1,382	1,382	—	—
Hypertension	401–404	41,463	509	1.282	1.12–1.44
Ischemic heart disease	410–414	257,845	1,562	0.632	0.60–0.67
Diseases of pulmonary circulation	415–417	12,062	89	0.719	0.52–0.92
Other forms of heart disease	420–429	212,991	1,721	0.844	0.79–0.90
Total cardiovascular and hypertensive disorders		524,361	3,876	0.772	0.76–0.78
Diabetes mellitus	250	45,424	434	0.998	0.82–1.17
Malignant neoplasms of brain	191	12,037	428	3.712	3.27–4.16
Fall from stairs/ladders	880	1,263	15	1.24	0.8–1.68
Accidental drowning	910	3,698	154	4.356	2.67–6.07
Accidental mechanical suffocation	913	1,111	38	3.572	0.60–6.5
Motor vehicle accidents	810.0–829.9	44,027	86	0.204	0.15–0.26

ICD = International Classification of Diseases; PMR = Proportionate Mortality Ratio.

<table>
<tr><td colspan="15">Taylor J., Chadwick D., Johnson T. Risk of accidents in drivers with epilepsy. Journal of Neurology, Neurosurgery, and Psychiatry 1996; 60:621-627</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="4">6</td></tr>
<tr><td>√</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="4"></td></tr>
<tr><td>Research Question</td><td colspan="14">To estimate the risk motor vehicle crashes over a three-year period in drivers with a history of single seizures or epilepsy, and to compare them with a cohort of drivers from the general population.</td></tr>
<tr><td>Study Design</td><td colspan="14">Case-control study</td></tr>
<tr><td rowspan="3">Population</td><td>Inclusion Criteria</td><td colspan="13">Drivers with a history of single seizures or epilepsy (British Neurology Survey of Driving [BNSD] sample) and non-epileptic drivers followed by the Transport Research Laboratory [TRL].
TRL survey restricted to drivers aged 20 years and over</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Cases: N = 16,958 drivers with a history of single seizures epilepsy
Controls: N = 8888 non-epileptic drivers
There was slight preponderance of women in the TRL sample, and of men in the BNSD sample. Responders to the BSND were also slightly older despite the TRL survey being restricted to drivers aged 20 years and over. The BSND sample had more driving experience (as measured by the interval between passing the driving test and the year of survey). The pattern of driving habits over the previous year was broadly similar in the two samples, with a slight excess of non-drivers in BSND, and everyday drivers in TRL; this was reflected in the annual mileages which indicated that drivers in the TRL survey drove about 500 miles per year more than those in the BNSD survey.
See Table G-18 for complete details</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Retrospective survey of driving and crashes experience by self-completion questionnaire. The two surveys were carried out within a period of two years of each other.
Non-epileptic drivers (responding to a TRL survey): Questionnaires sent by post for self-completion. Basic demographic information (age, sex), year of passing the driving test (or approximate number of years driving, if uncertain), and information about (car and/or van) driving over the previous year (whether or not driven at any time, frequency of driving, and total miles driven) were collected. The questionnaire also requested information about crashes involvements as a driver during the previous three years.
Drivers with single seizures or epilepsy (responding to the BNSD survey): Questionnaire sent out with each invitation for renewal from the DLVA (Morriston, Swansea). Licenses were issued to people with a history of epilepsy for a restricted period of up to three years. Towards the end of each license period the DLVA contacted the driver concerned to invite license renewal. Questionnaire also sent to drivers with recent seizures. The questionnaire was based on the one used in the TRL survey, but supplemented with questions about the history of seizures (calendar year of the first, and most recent epileptic attack of any kind, whether attacks were preceded by a warning or aura, and any other medical conditions. In addition, responders were asked whether they were actually taking antiepileptic drugs. Information was requested about epileptic attacks warnings, or aura while actually driving, and whether this had ever resulted in a crash.
All forms were returned directly to the survey office in Liverpool by prepaid reply envelope. The response rate was 72% in the TRL survey and 71% in the BNSD.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">A logistic regression model was used with occurrence of any crash during the previous three years as the (binary) dependent variable, and seven covariates in addition to an indicator for group membership. Of the seven covariates, sex was binary, driving during the previous year was categorical (Table G-18 lists the first five categories under the variable), and the remaining five were grouped continuous, the grouping being necessary to limit the total number of possible covariate patterns. The five were age, in years, its square, annual mileage, years of driving experience, and its square. Age was included as a quadratic form to model the initial decline and subsequent rise in accident reported previously; years of driving experience were modeled in the same way to allow (non-monotonic) curvilinear effects, and annual mileage was logarithmically transformed to provide a monotonic (curvilinear) trend. Risks are reported for unadjusted estimates, and after adjustment for imbalances between age, sex, driving experience, and annual mileage.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Quality score: 6.9</td><td colspan="13">Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="4">Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>26</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">The risk of any crash, any crash producing an injury, and any crash producing a serious injury, over a three year period.</td></tr>
<tr><td>Results</td><td colspan="14">After adjustment for differences in age, sex, driving experience and mileage between the two populations there was no evidence of any</td></tr>
</table>

	overall increase in risk in the population of drivers with a history of epilepsy. However, there was evidence of an increased risk of more severe crashes in the population with epilepsy. The risk was increased by about 40% for serious injuries and there was evidence of a twofold risk of increase in non-driver fatalities. These increases seem largely explicable by the occurrence of seizures in this population during the three years of driving that the survey covered. The adjusted odds ratio for risk of crash involvement was 0.95 (95% CI 0.88-1.02). The adjusted relative risk for being involved in a crash resulting in injury is 1.1 (95% CI 0.91-1.3). The adjusted odds ratio for risk of serious injury was 1.33 (95% CI 1.01-1.76).
Authors' Comments	A population of drivers with a history of epilepsy has an increased risk of involvement in crashes resulting in serious injury or fatality and this increase is of the order of 40% (by comparison with the TRL sample). The acceptability of driving for people with a history of epilepsy should be determined by an acceptable risk of crashes resulting in injury or serious injury rather than overall crash rates. As people with epilepsy can drive after a 12 month seizure free period rather than the required two year period when this survey was undertaken, it is important to ascertain whether there is any increased risk of injury associated crashes with this policy.
Reviewers' Comments	One limitation of this study is that the authors combined participants who only had single seizures with those who had a history of epilepsy. In addition, although the authors made adjustments for important factors such as age, gender, driving experience and annual mileage, they did not specify whether participants in either group were screened for comorbid medical conditions.

Table G-18. Demographic Characteristics and Driving Habits in the Two Surveys

	TRL Sample *n (%)*	*BNSD* *n (%)*
Total No	8888	16 958
Sex:		
Male	4310 (48)	9219 (54)
Female	4578 (52)	7708 (46)
Not known		31 (< 1)
Age (y):		
Median	32	38
(25, 75th centiles)	(22, 52)	(29, 49)
Not known		53 (< 1)
Driving experience (y):		
Median	9	12
(25, 75th centiles)	(3, 19)	(5, 22)
Not known	60 (< 1)	2541 (15)
Driven during past year:		
No	199 (2)	760 (4)
< Once a week	403 (5)	744 (4)
About once a week	305 (3)	615 (4)
Two or three times a week	1746 (20)	2677 (16)
Every day	6216 (70)	11 753 (68)
Not known	19 (<1)	409 (2)
Total miles driven in past year (× 1000)		
Median	6·0	6·0
(25, 75th centiles)	(2·5, 12)	(2·0, 10)
Median (excluding not driven)	6·6	6·0
(25, 75th centiles)	(2·8, 12)	(2·5, 11)
Not known	153 (2)	1288 (7)

Table G-19. Distribution of respondents by accident involvement during previous three years

No of accidents	TRL Sample n (%)	BNSD Recorded* n (%)	BNSD Corrected† n (%)
0	6860 (77)	13 349 (81)	13 344 (81)
1	1627 (18)	2410 (15)	2314 (14)
2	316 (4)	505 (3)	500 (3)
3	60 (< 1)	107 (< 1)	213 (1)
4	11 (< 1)	16 (< 1)	16 (< 1)
5	10 (< 1)	8 (< 1)	8 (< 1)
6	3 (< 1)	1 (< 1)	1 (< 1)
7	1 (< 1)		
Total known	8888	16396	16396
Not known		562 (3)	562 (3)
Total	8888	16958	16958
mean	0·29	0·23	0·25
Variance	0·37	0·30	0·35

*Number of accidents stated on survey form.
†Number of accidents after adjustment for those for which detail provided—see text.

Table G-20. Distribution of respondents by Accidents and Extent of Injury

Accidents and injuries	*TRL sample*	*BNSD*
No accidents in a car or van	6905 (78)	13 361 (81)
Car or van accidents	1983 (22)	3035 (19)
Without physical injury	1696 (86)	2566 (85)
Slight physical injury	202 (10)	285 (9)
Serious physical injury	82 (4)	164 (5)
Extent of injury unknown	3 (< 1)	20 (< 1)
Subtotal known	8888	16 396
Not known		562 (3)
Total	8888	16 958

Values in parentheses are percentages of subtotal known, except those in bold which are percentages of respondents involved in car/van accidents. Slight injury indicates cuts and bruises (for example), whereas serious injury was defined as needing hospital care.

Table G-21. Risk Factors for Accidents Three Years Before the Surgery

Covariate	*Any accident*	*Injury producing accident*	*Serious physical injury*
Has warning or aura	1·08 (0·99, 1·17)	1·16 (0·95, 1·41)	1·34 (0·96, 1·87)
Taking antiepileptic drugs	1·10 (1·01, 1·20)	1·00 (0·81, 1·21)	0·75 (0·54, 1·04)
Period seizure free > 3 years	0·74 (0·62, 0·87)	0·66 (0·46, 0·93)	0·56 (0·32, 0·96)

Values are OR (95% CI).

Table G-22. Mortality Statistics: 1992

	Men	*Women*	*Total*
Deaths (E810–E819)	2848	1210	4058
Deaths (E820–E825)	45	11	56
Total	2893	1221	4114
Estimated population aged 20–79 years (× 1000)	17 851·2	18 480·1	36 331·3
Deaths/100 000/y			11·32
	TRL sample	*BNSD*	
Total	8888	16 958	
No accident information	—	562	
Accident information	8888	16 396	
Expected fatalities	3·0	5·6	
Observed (reported)	—	12	

Source: series DH4 No 18. [11]

<table>
<tr><td colspan="15">Reference: Vernon DD, Diller EM, Cook LJ, Reading JC, Suruda AJ, Dean JM. Evaluating the crash and citation rates of Utah drivers licensed with medical conditions, 1992-1996 Accident Analysis and Prevention 34 (2002) 237-246.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="2">6</td></tr>
<tr><td>√</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="13">Objective: To compare the rates of adverse driving events (crash, at-fault crash and citations) experienced by drivers with medical conditions to those of age- sex- and location- matched controls. Medical conditions included a cardiovascular category.</td></tr>
<tr><td>Study Design</td><td colspan="13">Retrospective Case-control</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="12">• Drivers identified by the Utah Driver License Division as medical condition drivers, and categorizing their conditions and functional ability over time. The Utah condition category of Epilepsy includes other episodic conditions include syncope, cataplexy, narcolepsy, hypoglycemia, and episodic vertigo that interferes with function.
• For each driver with a medical condition two control drivers of the same age group, sex and place of residence were selected randomly from all licensed drivers, excluding commercial drivers.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="12">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="12">• N=2,739 epileptic licensed drivers.
• See Table G-23.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="12">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="13">• Authors obtained data on dates and types of licensure, renewal dates, medical conditions, and citation data from the Utah Driver License Division. Motor vehicle crash data was obtained from the Utah Department of Transportation and death certificate data from the Utah Department of Health database. Probabilistic linkage methodology was used to link the databases for analysis.
• Medical conditions were divided into two groups based on Utah's licensing program. These were non-restricted (licensing periods shortened) and restricted (limits on speed, time of day, area, etc.).</td></tr>
<tr><td>Statistical Methods</td><td colspan="13">Rates of citation, crashes and at-fault crashes were expressed as events per 10,000 license days, calculated separately for medical condition drivers and corresponding comparison groups. This was done for each medical category and restriction status. Based upon a chi-squared distribution, these data were used to determine an estimate of relative risk based upon one degree of freedom and a 95% confidence level.</td></tr>
<tr><td rowspan="5">Quality assessment</td><td rowspan="5">Internal Validity</td><td colspan="13">Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>26</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="13">Relative risk of crash, at -fault crashes and citation in epileptic group.</td></tr>
<tr><td>Results</td><td colspan="13">• Accidents and at -fault accident rates in the epileptic group were not significantly different from controls While both restricted and unrestricted drivers had higher rates of crashes and at fault crashes (R.R. 1.47-2.39). See tables Table G-24, Table G- 25, and Table G-26.
• The most license status changes occurred in drivers with epilepsy and other episodic conditions (27%).</td></tr>
<tr><td>Authors' Comments</td><td colspan="13">• One limitation was that the study could not control for exposure. Authors thought that drivers in the same age group would drive approximately the same number of miles/year.</td></tr>
<tr><td>Reviewers' Comments</td><td colspan="13">Author states that possible underreporting of medical conditions and accurate assessment of exposure rates are potential weaknesses in the program.</td></tr>
</table>

Table G-23. Restriction status of drivers reporting single medical conditions, Utah 1992-1996

Category	Stable restriction status			Fluctuating level	Total number	Percent of total (%)
	Not restricted	Restricted	No driving permitted			
Diabetes	9731	31	4	339	10 105	18
Cardiovascular	18 865	41	8	125	19 039	35
Pulmonary	2437	69	4	178	2688	5
Neurological	773	79	11	119	982	2
Epilepsy	1893	71	30	745	2739	5
Learning, memory	102	3	23	6	134	<1
Psychiatric	6481	42	3	282	6808	12
Alcohol and drugs	124	5	1	19	149	<1
Visual acuity	10 116	1279	25	263	11 683	21
Musculoskeletal	353	15	1	17	386	1
Functional motor	208	8	3	6	225	0
Total number	51 083	1643	113	2099	54 938	100
Percent of total (%)	94	3	0.2	4		

Table G-24. Relative risk for citations, drivers reporting single medical conditions versus control drivers, Utah 1992-1996

	Restriction status	Rate per 10 000 license days		RR[a]	LCL[b]	UCL[c]
		Medical conditions	Controls			
Diabetes	Not restricted	2.61	2.55	1.02	0.98	1.07
	Restricted	4.43	3.20	1.39	0.92	2.09
Cardiovascular	Not restricted	1.23	1.62	0.76	0.72	0.80*
	Restricted	3.14	1.98	1.58	0.74	3.38
Pulmonary	Not restricted	2.24	2.56	0.87	0.79	0.97*
	Restricted	0.69	1.42	0.49	0.18	1.30
Neurological	Not restricted	2.11	2.31	0.92	0.76	1.10
	Restricted	1.64	2.16	0.76	0.44	1.29
Epilepsy	Not restricted	4.06	3.97	1.02	0.96	1.10
	Restricted	4.13	3.92	1.05	0.81	1.36
Learning, memory	Not restricted	4.81	3.82	1.26	0.85	1.86
	Restricted	20.57	1.77	11.63	3.58	37.78*
Psychiatric	Not restricted	3.94	3.19	1.23	1.17	1.30*
	Restricted	3.25	3.86	0.84	0.53	1.33
Alcohol and drugs	Not restricted	8.46	3.55	2.38	1.82	3.12*
	Restricted	19.99	3.43	5.83	3.19	10.66*
Visual acuity	Not restricted	2.96	2.19	1.35	1.27	1.43*
	Restricted	1.80	1.38	1.31	1.10	1.56*
Musculoskeletal	Not restricted	2.36	1.93	1.22	0.90	1.65
	Restricted	0.00	2.16	Zero rate		
Functional motor	Not restricted	3.46	2.44	1.42	1.04	1.94*
	Restricted	0.00	2.90	Zero rate		

[a] RR: relative risk.
[b] LCL: 95% lower confidence limit.
[c] UCL: 95% upper confidence limit.
* Significantly different from control, $P<0.05$ (confidence interval does not include 1.0).

Table G- 25. Relative risk for all crashes, drivers reporting single medical condition versus control drivers, Utah 1992—1996

	Restriction status	Rate per 10 000 license days		RR[a]	LCL[b]	UCL[c]
		Medical Conditions	Controls			
abetes	Not restricted	1.70	1.30	1.30	1.23	1.38*
	Restricted	2.03	1.47	1.38	0.75	2.54
rdiovascular	Not restricted	1.04	1.05	0.99	0.93	1.06
	Restricted	1.35	0.98	1.37	0.43	4.38
lmonary	Not restricted	1.52	1.29	1.18	1.03	1.34*
	Restricted	1.04	1.14	0.91	0.40	2.09
urologic	Not restricted	1.90	1.17	1.62	1.32	1.99*
	Restricted	1.75	1.31	1.33	0.78	2.28
ilepsy	Not restricted	2.69	1.55	1.73	1.58	1.90*
	Restricted	2.67	1.81	1.47	1.06	2.03*
arning, memory	Not restricted	3.31	1.51	2.19	1.33	3.61*
	Restricted	5.14	0.00			
chiatric	Not restricted	2.24	1.43	1.57	1.46	1.67*
	Restricted	2.57	1.37	1.87	1.11	3.17*
cohol and drugs	Not restricted	3.09	1.70	1.82	1.18	2.81*
	Restricted	9.99	2.37	4.21	1.80	9.85*
ual acuity	Not restricted	1.75	1.30	1.35	1.25	1.46*
	Restricted	1.40	1.10	1.27	1.04	1.55*
sculoskeletal	Not restricted	1.64	1.03	1.59	1.10	2.29*
	Restricted	2.22	0.49	4.51	1.01	20.12*
ctional motor	Not restricted	1.56	1.41	1.11	0.70	1.74
	Restricted	0.00	1.69			

RR: relative risk.
[b] LCL: 95% lower confidence limit.
UCL: 95% upper confidence limit.
[a] Significantly different from control, $P<0.05$ (confidence interval does not include 1.0).

Table G-26. Relative risks for all fault crashes, drivers reporting single medical condition versus control drivers, Utah 1992-1996

	Restriction status	Rate per 10 000 license days		RR[a]	LCL[b]	UCL[c]
		Medical Conditions	Controls			
Diabetes	Not restricted	1.02	0.70	1.46	1.36	1.58*
	Restricted	1.48	0.83	1.77	0.87	3.61
Cardiovascular	Not restricted	0.55	0.55	1.00	0.92	1.09
	Restricted	0.90	0.58	1.54	0.37	6.40
Pulmonary	Not restricted	0.85	0.68	1.26	1.06	1.50*
	Restricted	1.04	0.65	1.60	0.69	3.71
Neurological	Not restricted	1.32	0.60	2.20	1.71	2.84*
	Restricted	1.09	0.78	1.40	0.71	2.76
Epilepsy	Not restricted	1.76	0.87	2.02	1.80	2.27*
	Restricted	2.40	1.00	2.39	1.70	3.36*
Learning, memory	Not restricted	2.56	0.77	3.32	1.84	5.99*
	Restricted	5.14	0.00			
Psychiatric	Not restricted	1.37	0.75	1.85	1.69	2.01*
	Restricted	2.22	0.77	2.89	1.64	5.07*
Alcohol and drugs	Not restricted	1.83	0.82	2.22	1.25	3.94*
	Restricted	8.33	1.45	5.75	2.26	14.61*
Visual acuity	Not restricted	1.15	0.75	1.52	1.38	1.68*
	Restricted	1.17	0.75	1.56	1.25	1.94*
Musculoskeletal	Not restricted	0.98	0.53	1.84	1.14	2.98*
	Restricted	2.22	0.20	11.29	2.39	53.25*
Functional motor	Not restricted	1.22	0.71	1.71	1.00	2.93
	Restricted	0.00	1.21			

[a] RR: relative risk.
[b] LCL: 95% lower confidence limit.
[c] UCL: 95% upper confidence limit.
* Significantly different from control, $P<0.05$ (confidence interval does not include 1.0).

<table>
<tr><td colspan="15">Reference: Waller, JH Chronic Medical Conditions and Traffic Safety: Review of the California Experience. NEJM 1965 273:1413-1420.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="3">6</td></tr>
<tr><td>√</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="3"></td></tr>
<tr><td>Research Question</td><td colspan="14">Do drivers with known medical conditions have higher accident and violation rates than drivers not known to have these medical conditions? (Epilepsy included as category.)</td></tr>
<tr><td>Study Design</td><td colspan="14">Case-control</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Cases - A sample of 2672 consecutive persons with known chronic medical conditions whose records were under review by the Department of Motor Vehicles. Controls (926) were from a random sample of California drivers (total =7500) who filled out a questionnaire given to all renewal applications on June 6, 1963.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">See Table G-28.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">All licensed-drivers and age groups included in study.</td></tr>
<tr><td>Procedures</td><td colspan="14">Observed and expected three year accident and violation rates of the control group were compared to those with different medical conditions (epilepsy). Rates were age-adjusted.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Authors calculated the significance of the difference between observed and expected accident and violation rates. Significance of difference was determined by Mann-Whitney U test.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td colspan="13">Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="4"></td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>26</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Expected and observed rates of accidents and violations/ 1,000,000 miles. (age-adjusted)</td></tr>
<tr><td>Results</td><td colspan="14">See Table G-27 Expected accidents for epilepsy group = 8.2 / 1 million miles and observed =16.0 /1 million miles. Difference significant at 0.001 level. Expected violation rate =3.4/ 1million miles and observed =4.7/ 1 million miles. Difference significant at p<.005.</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">• Author also suggested that severity of the illness is a very important consideration. The analyst who estimates accident risk is more concerned with loss of consciousness or conscious control rather than long-term medical prognosis. For a medical restriction program to be successful, the driver's attitude is important. A negative attitude was defined as driving with a revocation or ignoring medical regimen.
• Drivers with Epilepsy and other medical/mental conditions average twice as many accidents per 1,000,000 miles of driving; one and three tenths to one and eight tenths times as many violations per 100,000 miles as driving in the age adjusted comparison group. See Table G-30
• The results of the study pertaining to epilepsy as a major handicap is too narrow an approach.</td></tr>
<tr><td>Reviewers' Comments</td><td colspan="14">• Epilepsy was defined as a history of episodes of loss of consciousness or conscious control because of an intracranial lesion instead of just lesion of cerebral blood vessel.
• Table G-29, includes causes of traumatic Epilepsy in 165 persons included in this study reviewed by the California Department of Motor Vehicles (DMV).
• Accuracy is difficult to measure since study narrows to include an Epileptic population known to DMV</td></tr>
</table>

Table G-27. Observed and expected three-year accident and violation rates according to the Diagnostic Category for Drivers with Medical Conditions Reviewed by the California Department of Motor Vehicles.

Diagnostic Category	Driving Exposure	Accidents		Violations	
		Expected*	Observed†	Expected*	Observed†
	1,000,000 mi.	*/1,000,000 mi.*	*/1,000,000 mi.*	*/100,000 mi.*	*/100,000 mi.*
Epilepsy (445)‡	11.1	8.2	16.0	3.4	4.7
Cardiovascular disease (216)‡	5.5	9.0	14.6	2.7	3.6
Diabetes (257)	9.0	8.7	15.5	3.3	4.6
Alcoholism (261)	8.2	6.8	11.3	2.5	4.6
Drug usage (306)‡	10.4	8.4	8.6	3.6	6.4
Mental illness (231)	6.9	7.2	15.3	3.0	5.3
Miscellaneous (86)	2.2	7.4	20.7	2.8	4.9

Table G-28. Mean and median ages of Males and Females with Medical Conditions Reviewed by the California Department of Motor Vehicles and of a Comparison Sample of California Drivers Not Know to have Medical Conditions.

Diagnostic Category	Males			Females		
	Number	Mean Age	Median Age	Number	Mean Age	Median Age
		yr.	*yr.*		*yr.*	*yr.*
Comparison sample	511	42.7	42	411	42.5	41
Epilepsy	414	36.7	35	166	39.8	30
Cardiovascular disease	197	58.5	59	34	52.2	52
Diabetes	214	42.1	41	73	38.1	36
Alcoholism	279	46.7	47	40	44.5	42
Drug usage	306	30.8	29	46	34.2	32
Mental illness	194	36.7	36	98	40.0	40
Miscellaneous	77	70.9	51	22	39.8	36

Table G-29. Stated Cause of Epilepsy in 165 Persons with Traumatic Epilepsy reviewed by the California Department of Motor Vehicles

Stated Cause	Percentage
Trauma — type not stated	19
Automobile, cycle or pedestrian accident	35
Struck by object or caught in equipment	12
Fall	11
Sports injury	6
War injury	6
Assault	5
Civilian gun injury	2
Injury from horse	2
Birth trauma	2
Total	100

Table G-30. Average Annual miles of Driving Exposure for Persons with Medical Conditions Reviewed by the California Department of Motor Vehicles and for a Comparison Sample of California Drivers Not Known to Have Medical Conditions

	Males	Females	Total*	Males	Females
Comparison sample	898	748	1,646	13,100	5,000
Epilepsy	330	117	447	8,700	5,400
Cardiovascular disease	188	30	218	8,400	6,100
Diabetes	200	57	257	12,600	5,200
Alcoholism	227	34	261	10,800	5,800
Drug usage	266	42	308	12,000	6,500
Mental illness	153	78	231	11,000	5,500
Miscellaneous	66	18	84	9,900	4,200

*Medical groups add up to 1,808 instead of 2,160 because 352 persons had no licenses or had licenses revoked during 2 or more yr. immediately before current report.

Study Summary Tables for Key Question 2

No studies met the inclusion criteria for this Key Question.

Study Summary Tables for Key Question 3

Reference: Eliashiv SD, Dewar S, Wainwright I, Engel J, Fried I. Long-term follow-up after temporal lobe resection for lesions associated with chronic seizures. Neurology 48:1383-1388 (1997).

Key Questions Addressed	**1**	**2**	**3**	**4**	**5**	**6**
			X			

Research Question	This study reports the UCLA experience with 60 individuals who underwent uniform en bloc anterior temporal lobe resection for chronic seizures associated with temporal lobe lesions.	
Study Design	Prospective Case Series	
Population	**Inclusion Criteria**	All individuals had experienced seizures for at least 2 years prior to surgery. Only individuals with follow-up greater than 1 year postsurgery were included in the study.
	Exclusion Criteria	None Reported
	Study population Characteristics	Gender: 27 (M), 33 (F) Mean age at onset: 15 years (median = 13.5 years) Mean duration of epilepsy: 13 years Follow-up duration: 1 – 30 years (mean = 8.4 years, median = 6 years) 41 individuals (68%) had surgery on the right hemisphere and 19 (32%) on the left
	Generalizability to CMV drivers	Unclear
Methods	The presurgical work-up for all individuals included a comprehensive neurologic examination, a neuropsychological battery, and neuroradiologic studies. All individuals included in this study underwent uniform en bloc temporal lobe resection. Charts were abstracted for age of seizure onset, length of time individuals experienced seizures before proceeding to surgery, presence or absence of preoperative auras, side of surgery, age at surgery, pathology as determined by the histopathologic report, and all recorded follow-up, including radiologic studies. In addition to chart review, follow-up telephone interviews were conducted with 82% of the individuals. The interview was structured to include verification of age of seizure onset, risk factors for epilepsy, preoperative auras, postoperative tumor recurrence in the glial tumor group, and current living status. In addition, questions were asked about the occurrence of postoperative seizures, including current seizure frequency and pattern, persistence of auras, and the use of AEDs. A designation of "seizure-free" outcome was given to those who were experiencing no seizures on follow-up, although such individuals may have had residual auras or they may have experienced seizures immediately following surgery or on withdrawal of medications.	
Statistical Methods	Seizure outcome was assessed using the Kaplan-Meier analysis. Kaplan-Meier curves were compared using a log-rank test, which yielded a chi-square statistic and corresponding p-value.	

Quality assessment														
	Study quality=6.8	1	2	3	4	5	6	7	8	9	10	11	12	13
		Y	NR	Y	Y	Y	N	N	Y	Y	NR	Y		
	Low	14	15	16	17	18	19	20	21	22	23	24	25	

Relevant Outcomes Assessed	Seizure control following surgery
Results	A Class I outcome (seizure-free) was found for 83% of the 60 individuals at 1 year postresection. The Kaplan-Meier curve used to assess the likelihood of being seizure-free at intervals after surgery is shown in Figure G-1. On this basis the probability of being seizure-free was 80% (SE, 11.4%) at the median 6 years of follow-up. Duration of illness prior to surgery was found to have a significant influence on postoperative seizure outcome. Individuals with a relatively short history of seizures (2 – 12 years) showed a 90% (SE, 6%) of remaining seizure-free for 6 years after surgery, as compared with 68% probability (SE, 10%) for individuals with a seizure duration greater than 12 years (see Figure G-2). This group had an increasingly worse prognosis, with only about 50% likely to remain seizure-free after 10 years. The difference between the Kaplan-Meier curves of the two groups was statistically significant (p = 0.06).
Authors' Comments	This study confirms that anterior temporal lobe resection for temporal lesions associated with chronic seizures is a successful treatment with a high seizure-free rate following surgery and good psychosocial outcome.

Figure G-1. Postoperative Seizure Free Status over Time (Kaplan-Meier Analysis)

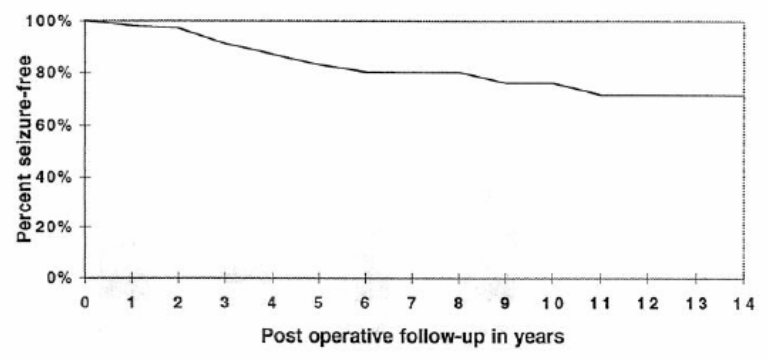
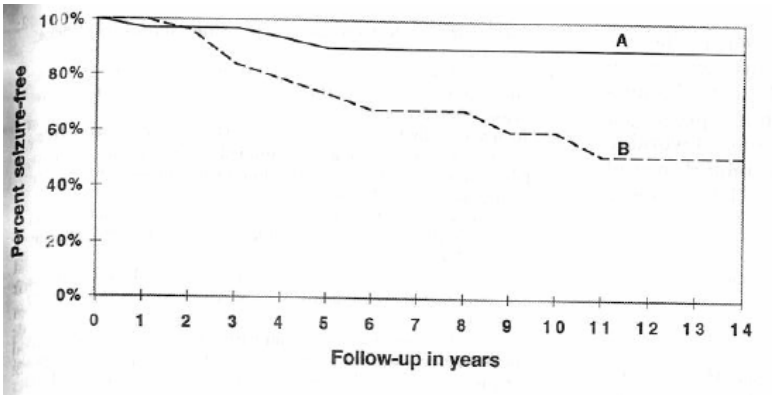


Figure G-2. Preoperative Seizure History Duration and Postoperative Seizure Free Status over time (Kaplan-Meier Analysis)



<table>
<tr><td colspan="9">Reference: Foldvary N, Nashold B, Mascha E, Thompson EA, Lee N, McNamara JO, Lewis DV, Luther JS, Friedman AH, Radtke RA. Seizure outcome after temporal lobectomy for temporal lobe epilepsy. Neurology 2000; 54: 630-634</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td colspan="2"></td></tr>
<tr><td></td><td></td><td>√</td><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="8">To determine seizure outcome and its predictors in patients wit medically refractory temporal lobe epilepsy (TLE) after temporal lobectomy (TL).</td></tr>
<tr><td>Study Design</td><td colspan="8">Prospective Case Series</td></tr>
<tr><td rowspan="3">Population</td><td>Inclusion Criteria</td><td colspan="7">Patients who underwent TL at the Duke University Medical Center from 1992 through 1984</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="7">Patients with less than 2 years of follow-up.
Patients with degenerative disorders.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="7">Population (N): 79
Sex (patients):
57% males
43% female
Mean age (± SD) at the time of surgery (years):
23.9 ± 9
Duration of epilepsy (years):
12.9 ± 8.5</td></tr>
<tr><td></td><td>Generalizability to CMV drivers</td><td colspan="7">Unclear</td></tr>
<tr><td>Methods</td><td colspan="8">• Surgical candidacy was based on clinical history, neurologic examination, and interictal EEG recordings in all patients.
• Age at surgery, duration of seizure disorder, gender, side of resection, recorded seizures during routine or prolonged EEG, and monthly CPS frequency were analyzed as predictors of seizure outcome.
• Outcome obtained by medical chart review and when possible, telephone contact with patient or an immediate family member
• Primary outcome of interest were time to first seizure and time to first year with less than 75% improvement from baseline in number of seizures per year.
• Seizure outcome during the entire follow-up period was classified using Engel's classification:
o Class I includes subjects who are SF with or without auras, those with generalized seizures after antiepileptic drug (AED) withdrawal, and subjects who are SF for 2 years or more after at least one postoperative seizure.
o Class II includes patients with rare seizures.
o Class III is defined as a 75% or greater reduction in seizures
o Class IV includes patients with less than 75% seizure reduction.
• Data considered absent when patients did not return for follow-up.
o Of 79 patients, annual seizure data were available for all years of follow-up in 77 patients
o In two patients, data was missing for 6 and 8 years during follow-up periods of 21 and 18 years respectively.
Compare Figure G-3and Figure G-4</td></tr>
<tr><td>Statistical Methods</td><td colspan="8">Predictors of seizure outcome analyzed using Kaplan-Meier survival analysis to obtain estimates and 95% confidence intervals (CIs) of SF survival and survival from experiencing a year with less that 75% improvement form baseline at various postoperative intervals.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Study quality = 7.5</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td>NR</td><td>Y</td><td></td><td></td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="8">Seizure frequency measured in patients postoperatively following temporal lobe (TL)</td></tr>
<tr><td>Results</td><td colspan="8">• The mean follow-up was 14.0 years (range, 2.1 to 33.6 years0
• At the time of last follow-up, seizure outcome classification was class I, 51 (65%); class II 12 (15%), class III, 9 (11%): and class IV, 7 (9%).
• 28 Patients (35%) were entirely SF and I (10% had auras only.
• 43 additional patients (55% experience at least one recurrent seizure and 30 of them (38% experience multiple seizures).
• Seizures recurred within 1 month in 19% of patients (8 of 43), by 6 months in 56% of patients (24 of 43), by 12 months in 67% of patients (29 of 43, and by 24 months in 86% of patients (37 of 43.
• The latest recurrence to place 300 months postoperatively after AED withdrawal; in 2 of these patients, no additional seizure</td></tr>
</table>

	occurred. • SF survival at 5, 7, and 10 years beyond the 12 and 24 month postoperative landmarks stratified by SF status at the landmark is shown in Table G-31 • SF estimates of 72%, 67%, 56% and 50% at 6 months and 1, 5, and 10 years were observed in subjects wit less than 20 seizures per month compared with 50%, 44%, 28%, and 17% for patients wit more than 20 seizures per month. • Patients with recorded seizures during routine or prolonged EEG (n=37) had similar seizure outcome to those who did not (n=42, p=0.73). • Refer to Table G-32 for additional information.
Authors' Comments	• In our series, patients with more than 20 seizures per month were less likely to become SF than those with less frequent seizures. • Fewer patients had long-term follow-up document adequately due to changes in 1984 when there was a change of staff in the epilepsy center which included the surgeon who performed the majority of the procedures. Therefore, patients were excluded from study if operated after 1984. • Study had two major limitations, one of which includes lack of video-EEG monitoring, structural and functional neuroimaging, and neuropsychological assessments in all patients. • Author believes that this series is a valuable one, demonstrating the long-term benefit of TL in patients with refractory arising from the temporal lobe.

Figure G-3. Kaplan-Meier estimates of postoperative seizure-free (SF) survival by early landmark

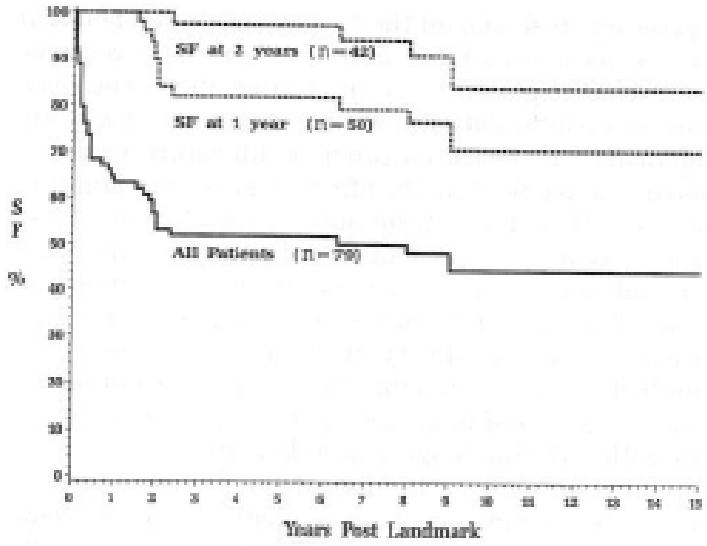


Figure G-4. Kaplan-Meier analysis of preoperative seizure frequency in quartiles of data

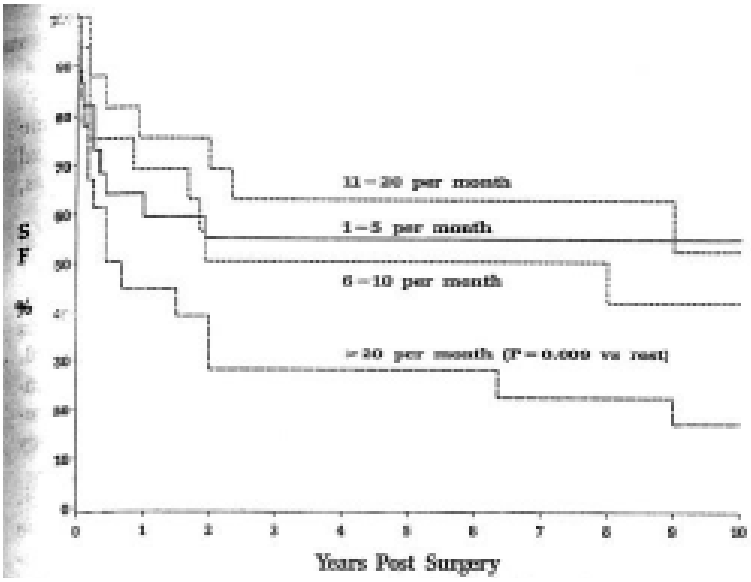


Table G-31. Early status as indicator of seizure-free (SF) survival

			SF survival after landmark, Kaplan–Meier percent (95% CI)		
Landmark	Still SF	n (%, of 79)	5 y	7 y	10 y
Surgery	Yes	79 (100)	52 (41–63)	50 (39–61)	45 (33–56)
12 mo	Yes	50 (63)	82 (71–93)	77 (64–89)	71 (57–85)
	No	29 (37)	31 (14–48)	27 (11–44)	27 (11–44)
	Total	79 (100)	63 (53–74)	58 (47–70)	55 (43–66)
24 mo	Yes	42 (53)	95 (87–100)	84 (71–97)	84 (71–97)
	No	37 (47)	33 (18–49)	30 (15–46)	30 (15–46)
	Total	79 (100)	65 (54–76)	58 (47–70)	58 (47–70)

Table G-32. Early status as indicator of < 75% improvement survival

Landmark	Still SF	n (%, of 78)*	Freedom from <75% reduction after landmark, Kaplan–Meier percent (95% CI) 5 y	7 y	10 y
Surgery	Yes	78* (100)	87 (79–94)	87 (79–94)	85 (77–93)
12 mo	Yes	50 (64)	100 (100–100)	100 (100–100)	97 (92–100)
	No	28 (36)	64 (47–82)	64 (47–82)	59 (40–78)
	Total	78 (100)	87 (79–94)	87 (79–94)	83 (74–92)
24 mo	Yes	42 (54)	100 (100–100)	97 (90–100)	97 (90–100)
	No	36 (46)	74 (59–88)	74 (59–88)	69 (53–85)
	Total	78 (100)	88 (80–95)	86 (78–94)	84 (75–93)

* One patient could not be evaluated because of unknown preoperative monthly seizure frequency.

SF = seizure free.

Reference: Jeha LE, Najm IM, Bingaman WE, Khandwala F, Widdess-Walsh P, Morris HH, Dinner DS, Nair D, Foldvary-Schaeffer N, Prayson RA, Comair Y, O"Brien R, Bulacio J, Gupta A, Lűders HO. Neurology 2006;66:1938-1940														
Key Questions Addressed	1	2	3	4	5	6								
			X											
Research Question	To assess short- and long-term seizure freedom in patients after temporal lobectomy for treatment of intractable epilepsy.													
Study Design	Prospective Case Series													
Population	**Inclusion criteria**	(1). Patients with more than 1 year follow-up who underwent anterior temporal lobectomy (2). Patients without any prior history of brain surgery												
	Exclusion criteria	(1). Patients with less than 1 year follow-up (2). Patients with previous brain surgery (3). Patients with incomplete records												
	Study population characteristics	Adult patients who underwent anterior temporal lobectomy between 1990 and 2001 to treat pharmacoresistant epilepsy.												
	Generalizability to CMV drivers	Unclear												
Methods	All study subjects underwent scalp video-electroencephalogram (EEG) monitoring and high resolution magnetic resonance images (MRIs). After case discussion, 77 of 371 patients underwent additional evaluation with combinations of depth and subdural electrodes. Surgeries performed included selective amygdala-hippocampectomy; removal of mesial structures, temporal tip, and para hippocampal and inferior temporal gyri; or neocortical resection based on imaging and invasive EEG. Surgical pathology was obtained in all and outcome information was obtained from follow-up clinic visits.													
Statistical Methods	Using SAS 8.2 software, a multivariate hazard model was constructed, and its terms were assessed graphically by plotting the predicted probability of seizure recurrences as a function of significant risk factors. Additional analyses used multivariate logistic modeling to compute adjusted odds rations that quantify effects of various predictors in the first year.													
Quality assessment	Study quality=6.1	1	2	3	4	5	6	7	8	9	10	11	12	13
		Y	NR	Y	Y	Y	N	N	NR	NR	Y	Y		
	Low	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Seizure recurrence													
Results	The mean follow-up duration was 5.5 (range 1 to 14.1 years). Fifty-three percent of patients were seizure free at 10 years. Seizures recurred in 140 patients (37%). Most recurrences occurred early with a median timing of 6.6 months postoperatively: 62% of patients with recurrent seizures relapsed within the first year, and 94% relapsed within 5 years. Primary outcome did not correlate with age at epilepsy onset, age at surgery, epilepsy duration, or side resection. Early seizure freedom (no recurrence by 2 postoperative years) was decreased by frequent preoperative seizures, generalized tonic-clonic seizures, bilateral MRI abnormalities, the use of invasive EEG monitoring, and epileptiform discharges on EEG 6 months postoperatively (see Table G-33). Continuing seizure freedom beyond 2 years was lower when surgical pathology was restricted to gliosis and higher when intraoperative electrocorticography was used (see Table G-34).													
Authors' Comments	Results of EEG performed 6 months postoperatively correlated with occurrence and severity of seizure recurrence, in addition to breakthrough seizures with discontinuation of antiepileptic drugs.													
Reviewers' Comments	This study did not explore the different mechanisms of seizure recurrence, antiepileptic withdrawal, and the impact of various surgical techniques in the different etiologic subgroups.													

Table G-33. Predictors of Early Seizure Recurrence (within 2 postoperative years)

	Time since surgery		
	6 Months	1 Year	2 Years
Preoperative clinical characteristics			
Seizure frequency ($p = 0.015$)			
<20/month	89 (87–90)	84 (82–86)	79 (76–81)
>20/month	80 (76–84)	74 (69–78)	67 (62–72)
GTCs ($p = 0.029$)			
Absent	93 (91–95)	90 (87–93)	86 (82–89)
Present	85 (82–87)	79 (77–82)	74 (70–76)
Neuroimaging characteristics			
Bilateral MRI abnormalities ($p = 0.004$)			
Absent	88 (86–90)	83 (81–86)	78 (75–81)
Present	78 (66–80)	65 (57–73)	58 (49–67)
EEG characteristics			
Spikes on 6 months EEG ($p = 0.001$)			
Absent	90 (88–92)	86 (83–88)	81 (78–83)
Present	79 (74–82)	72 (67–76)	65 (60–70)
Invasive EEG evaluation ($p = 0.005$)			
Not done	89 (87–90)	84 (82–86)	79 (76–82)
Done	80 (75–83)	73 (68–77)	66 (61–71)

Predicted percentages of completely seizure-free patients (with 95% CIs) are shown at 6, 12, and 24 months.

GTCs = generalized tonic–clonic seizures.

Table G-34. Predictors of Late Seizure Recurrence (beyond 2 postoperative years)

	Time since surgery		
	2 Years	5 Years	8 Years
EEG characteristics			
Intraoperative ECOG ($p = 0.021$)			
Done	80 (77–83)	75 (70–78)	71 (66–75)
Not done	74 (72–77)	62 (58–65)	53 (48–57)
Pathologic characteristics			
Specific pathologic diagnosis ($p = 0.009$)			
Present	78 (75–81)	70 (67–73)	64 (60–68)
Absent (gliosis only)	71 (68–75)	56 (50–61)	44 (38–51)

Predicted percentages of completely seizure-free patients (with 95% CIs) are shown at 2, 5, and 8 years.

ECOG = electrocorticography.

<table>
<tr><td colspan="8">Reference: Jutila L, Immonen A, Mervaala E, Partanen J, Partanen K, Puranen M, Kälviäinen R, Alafuzoff I, Hurskainen H, Vapalahti M, Ylinen A. Long term outcome of temporal lobe epilepsy surgery: analyses of 140 consecutive patients. Journal of Neurology, Neurosurgery, and Psychiatry 73:486-494 (2002).</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td></tr>
<tr><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="7">The aims of this study were first, to analyze the long term outcome of temporal lobe epilepsy surgery with respect to seizures in a national epilepsy surgery center for adults; and second, to evaluate the preoperative factors that predict a good postoperative outcome on long term follow up.</td></tr>
<tr><td>Study Design</td><td colspan="7">Retrospective Case Series</td></tr>
<tr><td rowspan="4">Population</td><td colspan="2">Inclusion Criteria</td><td colspan="5">The authors analyzed all adult patients operated on for drug resistant temporal lobe epilepsy at their hospital since the beginning of the epilepsy surgery program, between 1988 and 1999.</td></tr>
<tr><td colspan="2">Exclusion Criteria</td><td colspan="5">The authors excluded patients with temporal lesionectomies (without amygdalohippocampectomy) and those in whom any extratemporal cortical excision had been carried out in addition to the temporal resection.</td></tr>
<tr><td colspan="2">Study population Characteristics</td><td colspan="5">Altogether 140 patients (67 women and 73 men) were included in the study. The median age of the patients at the time of the operation was 32 years (range 14 to 54). The median age at onset of epilepsy was 12 years (range 0.1 to 43) and median duration of epilepsy at the time of operation 19 years (range 2 to 47). Preoperative seizure frequency varied from 10 to 1655 seizures a year (median 78) during the year preceding the operation. In the majority of patients (82%, n = 115), most of the seizures were focal, with ictal impairment of consciousness and focal ictal EEG (median 75, range 7 to 916).
The preoperative clinical etiology of the epilepsy was probable symptomatic in 36% of the patients (n = 50) and symptomatic in 64% (n = 90). The symptomatic etiologies included hippocampal atrophy with no other etiology (28), asphyxia (15), central nervous system infection (13), tumoror cystic lesion (12), focal cortical dysplasia (9), brain contusion (5), and miscellaneous etiologies (8). In 10% of the patients (n = 14), first degree relatives had a history of epilepsy. Febrile seizures were identified in 21% of the patients (n = 30), and especially complex febrile seizures in 9% (n = 12).
On the basis of the preoperative assessment, 103 patients (74%) had unilateral temporal lobe epilepsy. Forty five patients had seizure onset on the left and 58 on the right. Thirty seven patients were operated on palliatively. These patients had bitemporal seizure onset (18), unitemporal but extratemporally extending seizure focus (6), multifocal epilepsy (2), dual pathology (2), combined temporal and extratemporal abnormality (2), bitemporal MR imaging abnormality (2), or posterior neocortical seizure onset in the dominant temporal lobe together with ipsilateral speech dominance (2). Three patients with temporal foreign tissue lesions without ictal EEG were also classified in the palliative group.
The operative procedures included anterior temporal resection and amygdalohippocampectomy alone (113) or combined with lesionectomy (9), and selective amygdalohippocampectomy (18).</td></tr>
<tr><td colspan="2">Generalizability to CMV drivers</td><td colspan="5">Unclear</td></tr>
<tr><td>Methods</td><td colspan="7">The data were collected retrospectively from the medical records of Kuopio University Hospital and the former Vaajasalo Hospital. The clinical etiology of the epilepsy was classified preoperatively as probable symptomatic or symptomatic (including patients with hippocampal atrophy in the MR imaging and no other obvious etiology). Seizure classification followed the ILAE task force on classification and terminology guidelines. Preoperative seizure frequency was calculated for the year preceding the operation, excluding seizures occurring during the video-EEG recording. Typical temporal lobe auras were not included in the seizure frequency; however, unclassified seizures (possibly including auras) were included.
The presurgical evaluation included a neurological examination, MR imaging, ictal video-EEG recording (136 recordings with scalp and sphenoidal electrodes, 50 recordings with subdural strip electrodes), neuropsychological evaluation (n = 135), a sodium amobarbital (WADA) test (n = 140), and psychiatric evaluation (n = 118).
The surgical procedure was classified as “curative” if preoperative assessment indicated unilateral temporal lobe epilepsy. However, if the patient had bitemporal or multifocal epilepsy, or if the epileptic focus could not otherwise be completely removed, the surgery was classified as “palliative.” Some patients with dual pathology (hippocampal atrophy in combination with an extrahippocampal structural lesion in the MR imaging), combined temporal and extratemporal abnormality (other temporal lobe lesion than hippocampal atrophy in association with an extratemporal lesion in the MR imaging), bitemporal MR imaging abnormality, or temporal foreign tissue lesion without ictal EEG, were also classified as palliative. In palliative patients only considerable postoperative seizure reduction, rather than freedom from seizures, was probable.
Patients from the primary Kuopio University Hospital district were followed up as outpatients since the operation. The patients referred from other parts of Finland were followed up as outpatients for three years. Routine visits were scheduled for all patients at three months, one year, and three years after the operation. In addition, each patient was contacted by telephone for further historical details and an up to date follow up. In problematic cases, medical records from other hospitals or community health centers were obtained. The original prospectively recorded seizure calendars were obtained whenever possible. Postoperative outcome was assessed according to a classification adapted from Engel. However, seizure-free patients and patients with postoperative auras only are displayed as two distinct groups following the suggestions of the new ILAE classification. Neighborhood seizures (seizures occurring one month postoperatively) were excluded from the analyses.
A complication was classified as major if it affected activities of daily living, lasted more than three months, or included any</td></tr>
</table>

	significant neurological deficit. Minor complications resolved within three months. Information on causes of death was acquired from the Finnish National Registry of Mortality.
Statistical Methods	The postoperative outcome was analyzed with the χ2 test for comparisons between patient groups, and with life tables. The predictive value of different preoperative factors with respect to outcome was assessed by logistic regression analysis. The demographic variables included history of (complex) febrile seizures, age at onset of epilepsy, duration of epilepsy, clinical etiology of epilepsy, preoperative seizure frequency (divided into subgroups by quartiles), seizure type predominance, and type of operation. Subgroups of qualitative MR imaging consisted of: hippocampal atrophy with or without temporal cortical atrophy; other unilateral structural abnormality in the temporal lobe; and other. All volumetric data for regression analyses were normalized. The preoperative ictal EEG was reclassified (by EM) for regression analyses into two subgroups consisting of unilateral mesial or temporal ictal onset, and other. A subset of neuropsychological tests evaluating the delayed visual or verbal memory was also chosen for analyses. A probability (p) value of less than 0.05 was considered statistically significant.
Quality assessment	Study quality = 6.4 (1 No; 2 Yes; 3 Yes; 4 Yes; 5 No; 6 No; 7 No; 8 Yes; 9 Yes; 10 Yes; 11 Yes) Moderate
Relevant Outcomes Assessed	Seizure relapses.
Results	The authors first analyzed the long term outcome in all patients (n = 140) using life tables. Eighty six per cent of all seizure relapses (71 of 83) occurred within one year of the operation. Late seizure relapses (> 2 years after the operation) were observed in only 5% of all patients (n = 7), and 8% of all relapses were late relapses. The majority of patients with late relapses had unilateral temporal lobe epilepsy with a symptomatic etiology (n = 6), and pathological examination showed hippocampal sclerosis (n = 5) or cortical microdysgenesis (n = 1). Late relapses were often preceded by a specific explanatory factor such as withdrawal of antiepileptic drug treatment (n = 3) or hyponatremia (n = 1), and they did not lead to subsequent intractable seizures in any of the patients. Initially 63% (n = 88) of all patients were seizure-free or had only postoperative auras at the first postoperative controls visit (three months postoperatively) (Table G-35). Fifty three percent of these remained completely free of seizures on long term follow up (mean (SD), 5.2 (2.6) years, range 1.0 to 10.5), whereas 5% experienced some seizures but again became seizure-free (for at least two years). In addition, 11% had only postoperative auras and 15% had rare seizures. Seventeen percent (n = 9) of patients with initial Engel II–IV outcome became free of seizures, and 8% (n = 4) had rare seizures on long term follow up (mean (SD), 4.9 (2.5) years, range three months to 10.0 years).
Authors' Comments	Eighty-six percent of the seizure relapses occurred within the first postoperative year. Late relapses were observed in 5% of patients, but these did not lead to subsequent seizure intractability. Late recurrences were associated with a symptomatic etiology of epilepsy, hippocampal sclerosis, and specific explanatory factors such as withdrawal of antiepileptic drug treatment. Follow up both at one and two years was highly predictive of the long term outcome, and most late recurrences were associated with hippocampal sclerosis or temporal lobe gliosis. In conclusion, most seizure relapses occur within two years of operation, and the outcome at one year or two years postoperatively is highly predictive of the long term outcome.

Table G-35. Postoperative Followup of Initially Seizure-Free Patients

Findings	3 m	1 y	2 y	3 y	4 y	5 y	7 y	9 y	Latest*
Seizure-free	76 (86)	56 (64)	44 (58)	40 (54)	31 (50)	26 (50)	13 (45)	6 (50)	51 (58)
Originally seizure-free	76 (86)	56 (64)	44 (58)	38 (51)	30 (48)	23 (44)	12 (41)	5 (42)	47 (53)
Became seizure-free†		0 (0)	0 (0)	2 (3)	1 (2)	3 (6)	1 (3)	1 (8)	4 (5)
Auras only	12 (14)	13 (15)	9 (12)	9 (12)	8 (13)	9 (17)	3 (10)	2 (17)	10 (11)
Engel II‡		13 (15)	10 (13)	9 (12)	11 (18)	10 (19)	5 (17)	2 (17)	13 (15)
Engel III‡		4 (5)	9 (12)	12 (16)	7 (11)	2 (4)	3 (10)	1 (8)	7 (8)
Engel IV‡		2 (3)	4(5)	4(5)	5 (8)	5(10)	5 (17)	1 (8)	7 (8)
Total	88 (100)	88 (100)	76 (100)	74 (100)	62 (100)	52 (100)	29 (100)	12 (100)	88 (100)

Values are n (%) of patients.
*Latest: latest available follow up data.
†Some seizures after surgery but now seizure-free for at least two years.
‡Engel II: fewer than three seizures a year; Engel III: worthwhile seizure reduction (at least an 80% seizure reduction); Engel IV: no worthwhile seizure reduction (less than 80% seizure reduction).
m, months; y, years.

Reference: Kelley K, Theodore WH. Prognosis 30 years after temporal lobectomy. Neurology 2005;64:1974-1976														
Key Questions Addressed	1	2	3	4	5	6								
			X											
Research Question	To assess the long-term outcome 30 years after temporal lobectomy													
Study Design	Retrospective Case Series													
Population	**Inclusion criteria**	Temporal lobectomy performed by Dr John Van Buren at the National institute of Health (NIH) from 1965 to 1974.												
	Exclusion criteria	Not Reported												
	Study population characteristics	Patients who had temporal lobectomy performed by Dr John Van Buren at the National institute of Health (NIH) from 1965 to 1974.												
	Generalizability to CMV drivers	Unclear												
Methods	Perioperatively patients underwent interictal electroencephalogram (EEG), skull x-rays, carotid arteriography, pneumoencephalography, neuropsychological testing, and intracarotid Amytal Sodium procedure. Surgery was performed under local anesthesia, and tailored resection was guided by electrocorticography. Care after the first postoperative year generally was provided by referring physicians; 95% of patients had yearly NIH visits until 1974.													
Statistical Methods	Data analysis was performed with Systat (SPSS, Chicago, IL). Analyses performed included parametric and nonparametric comparisons, logistic regression, and Kaplan-Meir analysis.													
Quality assessment	Study quality=4.3	1	2	3	4	5	6	7	8	9	10	11	12	13
		N	NR	NR	N	Y	N	N	Y	Y	NR	Y		
	Low	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Seizure recurrence													
Results	After a mean follow-up of 29.9 , 24 patients were seizure free, and 10 had died (see Table G-36). Early seizure recurrence and invasive EEG studies predicted worse long-term outcome. Patients with recurrence within the first year were less likely to be seizure-free at follow-up intervals. However, 12 seizure-free patients at current follow-up had a single seizure recurrence at some point in their course.													
Authors' Comments	The results of this study suggest a good prognosis for long-term seizure control after temporal lobectomy. Transient seizure recurrences may occur in the first few years after surgery, and there may be late recurrences even in patients seizure free for many years. Moreover, the results from the 1960s may suggest as well that excellent results can be achieved without ictal video-EEG recording, particularly when modern imaging studies are available.													
Reviewers' Comments	Reports in this study were subjective due to the fact that it was a retrospective and based on postoperative NIH clinic assessments and partly on patients' and families' report. Also prospective studies of surgical outcome over 30 years are difficult to perform as patients may be lost to follow-up or other life events.													

Table G-36. Characteristics of Enrolled Patients

Focus	Age at seizure onset, y	Presurgery duration, y	Age at surgery, y*	Resection size, cm†	Follow-up, y
Left temporal (22)	12.3 ± 11	20.1 ± 9.7	32.4 ± 11.5	5.14 ± 0.99	28.3 ± 5.9
Right temporal (26)	9.6 ± 5.6	16.5 ± 7.6	25.9 ± 7.1	6.8 ± 1.1	31.2 ± 3.5

* $p < 0.03$; † $p < 0.01$.

<table>
<tr><td colspan="15">Reference: Luders H, Murphy D, Awad I, Wyllie E, Dinner DS, Morris HH, Rothner AD. Quantitative Analysis of Seizure Frequency 1 Week and 6, 12 and 24 Months after Surgery of Epilepsy. Epilepsia 1994: 35(6): 1174-1178</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="2">6</td></tr>
<tr><td></td><td colspan="2"></td><td colspan="2">√</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="14">To determine a statistical significance in patients who have undergone resective procedures for partial seizures by measuring seizure-frequency following surgery.</td></tr>
<tr><td>Study Design</td><td colspan="14">Retrospective Case Series</td></tr>
<tr><td rowspan="3">Population</td><td>Inclusion Criteria</td><td colspan="13">Patients who have undergone localized resection for medically intractable partial seizures experienced through Cleveland Clinic Foundation (CCF)</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">Population:
n=71

Sex:
44 males
27 females

Type of Surgery (Number of patients)
Right temporal resection (28)
Left temporal resection (29)
Extratemporal resection (11)
Associated neoplasm (11)</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">• Follow-up observation points: preoperative period, 1 week and 6, 12 and 24 months postoperative. Refer to Table G-37.
• Seizure frequency was assessed by direct interview by one of the epileptologist at CCF and was recorded in the clinical chart; seizure frequency also considered if entered in computer registry (obtained by telephone interview by one of the nurse/clinicians) when assessing the outcome.
• Seizure free (SF) was defined as patients who had been seizure free ≥ 6 months at time of last follow-up; exception was patients who had seizure sin the first postoperative week but remained SF 6 months after operation
o Patients were also considered SF at 6-month postoperative time point.
o Patients who had only auras were also considered SF.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Chi-square test used to compare seizure frequency and analysis of variance with regard to the average number of seizures per month.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Study quality = 5.9</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>N</td><td>NR</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>NR</td><td>Y</td><td></td><td></td></tr>
<tr><td rowspan="2">Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Postoperative seizure frequency measured</td></tr>
<tr><td>Results</td><td colspan="14">• With a longer follow-up period the proportion of SF patients decreased progressively
• Data from patients who were SF (≥ 90% seizure decrease) and Patients with 90% seizure decrease were analyzed—none of the patients who had seizures at 6 or 12 months were SF at subsequent follow-up. Refer to Table G-38.
• Only 4 (7.1%) of the 56 SF patients at 6 months had <90% seizure decrease at 2-year follow-up; patients with seizures at 6 months did not become SF.
• Postoperative seizure outcome tended to be stable after 6 month follow-up except for a slight trend toward seizure recurrence in the initially SF group; trend continued for at least 2 years.
• Patients with ≥ 90% seizure decreased at 6 months continued to have seizures at 1 and 2 -year follow-up—many became part of < 90% seizure decrease group.
• 87% patients with no seizures in the first week remained SF at 6 months, and 77% were still SF at 2-year follow-up.
• Only 11% of patients with no seizures in the first week had < 90% seizure decrease at 2 years. See Table G-39.</td></tr>
</table>

	• Chi-square test used to compare seizure frequency at 6 months and 2 years showed a highly significant correlation (chi square= 56.6; p<0.01)
Authors' Comments	• Patients were SF at 1 year generally had an excellent prognosis, but with longer follow-up a small and certainly not negligible proportion of patients continued to develop seizures. • The progressive relapse of seizures apparently indicate that the remaining epileptogenic tissue becomes increasingly more active in time. • Author suggest that postoperative results should be reported at defined follow-up intervals to permit comparative studies. • Our result show that a good outcome at 6 months is highly predictive of a good outcome at follow-up periods ≥ 2 years. • Author could not differentiate between different types of seizures in the immediate postoperative period. • Information in patients charts was insufficient to allow reliable differentiation between the different types of seizures. • The lack of difference regarding outcome between patients with temporal and extratemporal epilepsy in this study may will be related to the rather small sample of extratemporal cases. Additional studies with a large number of extratemporal cases will be necessary to determine this issue.

Table G-37. Seizure outcome at 6, 12, and 24 months after resective surgery

Follow-up	Seizure-free, n (%)	Seizure reduction ≥90%, n (%)	Seizure reduction <90%, n (%)	Total, n (%)
6 mo	56 (79)	8 (11)	7 (10)	71 (100)
1 yr	53 (75)	8 (11)	10 (14)	71 (100)
2 yr	47 (66)	10 (14)	14 (20)	71 (100)

Table G-38. Seizure outcome in relation to 6-month postoperative seizure frequency

		Two years, n (%)		
Six months	One year, n (%)	SF	≥90% Seizure reduction	<90% Seizure reduction
SF (n = 56)	SF: 53 (95)	47 (84)	5 (9)	1 (2)
	≥90%: 2 (3)	0	0	2 (4)
	<90%: 1 (2)	0	0	1 (2)
≥90% Seizure reduction (n = 8)	SF: 0	0	0	0
	≥90%: 5 (63)	0	5 (63)	0
	<90%: 3 (37)	0	0	3 (37)
<90% Seizure reduction (n = 7)	SF: 0	0	0	0
	≥90%: 1 (14)	0	0	1 (14)
	<90%: 6 (86)	0	0	6 (86)

SF, seizure-free.

Table G-39. Seizure outcome 6 and 24 months postoperatively in patients with and without seizures in the first postoperative weeks

	Seizure-free n (%)	Seizure reduction ≥90%, n (%)	Seizure reduction <90%, n (%)
Six months			
One week			
+	10 (56)	4 (22)	4 (22)
−	46 (87)	4 (8)	3 (5)
			Chi-square 7.97
			df = 2
			0.05 significance = 5.99
Two years			
One week			
+	6 (33)	4 (22)	8 (44)
−	77 (41)	6 (11)	6 (11)
			Chi-square 12.54
			df = 2
			0.05 significance = 9.21

<table>
<tr><td colspan="15">Reference: McIntosh AM, Kalnins RM, Mitchell LA, Fabinyi GCA. Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. Brain. 2004;127:2018-2030</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td>3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="2">6</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td colspan="2"></td><td>X</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">To gain in-depth knowledge through examination of patterns of longitudinal outcome and potential risk factors for seizure recurrence after lobectomy.</td></tr>
<tr><td>Study Design</td><td colspan="14">Retrospective Case Series</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion criteria</td><td colspan="13">Patients who underwent anterior temporal lobectomy between 1978 and 1998.</td></tr>
<tr><td>Exclusion criteria</td><td colspan="13">(1). Patients with a history of previous surgery.
(2). Patients who had insufficient evidence on either magnetic resonance imaging (MRI) or histopathology to establish preoperative pathology.</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Three hundred and twenty-five patients at the Comprehensive Epilepsy Program, Austin Health.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">Surgery was performed by or under the direction of one of three surgeons. Over the period of the study, surgical technique was modified somewhat to restrict the amount of neocortex resected. Lesionectomy without hippocampal resection was performed for cases where the lesion was remote from a normal hippocampus.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Kaplan-Meir “survival” analysis was used to calculate the probability of seizure freedom and late seizure recurrence. Statistical significance was tested using the log-rank test and comparison of 95% confidence intervals. Potential risk factors for recurrence were examined using Cox proportional hazards models. Discontinuation of anti-epileptic drugs (AEDs) was analyzed as a time-dependent variable using Cox regression. Results were considered statistically significant at the 5% level.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Study quality=5.7</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>N</td><td>Y</td><td>NR</td><td>N</td><td>Y</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td></td><td></td></tr>
<tr><td rowspan="2">Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Seizure recurrence</td></tr>
<tr><td>Results</td><td colspan="14">Seizure recurrence after surgery occurred in 190 patients. In 48 patients, the “best” evidence pathology diagnosis (using all available evidence) differed from the histopathology (using temporal specimens alone). Seizure-free estimates are provided in more detail in Table G-40. Using univariate Cox regression procedures, a longer duration of epilepsy, later age at surgery and the presence of secondarily generalized seizures had statistically significant associations with poor outcome (see Table G- 41). After adjustment for “best evidence” preoperative pathology, the presence of preoperative generalized seizures had a significant association with postoperative seizure recurrence (see Table G-42).

The probability of complete seizure freedom at 2 years post-surgery was 55.3% (95% CI 50-61); at 5 years 47.7% (95% CI 42-53); and at 10 postoperative years it was 41% (95% CI 36-48). Duration of preoperative epilepsy, age of seizure onset and age at surgery did not have an effect on outcome.

Kaplan-Meier estimates of seizure freedom for all patients (including those with “distant lesions”) who were seizure free for 1 year (n= 118) and for 2 years (n= 178) following surgery were calculated (see Table G-43). The association of age of onset, duration of epilepsy, age at surgery and secondary generalized seizures with seizure recurrence (in patients seizure free for two postoperative years) was examined. These variables failed to reach statistical significance in the univariate analyses (see Table G-44). Details of AED discontinuation are contained in Table G-45. Survival analysis of the probability of seizure freedom from date of AED discontinuation was undertaken showed that seizure-free probabilities remained fairly high in both groups (see Table G-46).</td></tr>
<tr><td>Authors’ Comments</td><td colspan="14">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 as yet unidentified.</td></tr>
<tr><td>Reviewers’ Comments</td><td colspan="14">Clinical data from this study will inform preoperative decision making and pre- and postoperative patient counseling, rehabilitation and management. A prolong postoperative seizure-free period does not guarantee ongoing seizure freedom.</td></tr>
</table>

Table G-40. Probabilities of Seizure Freedom According to "Best Evidence Preoperative Pathology Diagnosis

Years post-surgery	Foreign tissue lesion (n = 51)			Hippocampal sclerosis (n = 201)			'Normal' pathology (n = 33)			Other (n = 16)			Distant lesion (n = 24)		
	Cases remaining in analysis	Probability seizure free (%)	95% CI	Cases remaining in analysis	Probability seizure free (%)	95% CI	Cases remaining in analysis	Probability seizure free (%)	95% CI	Cases remaining in analysis	Probability seizure free (%)	95% CI	Cases remaining in analysis	Probability seizure free (%)	95% CI
1 year	40	78.4	64.5–87.4	135	67.7	60.7–73.7	8	24.2	11.5–39.6	5	31.2	11.4–53.7	9	37.5	19.0–56.0
2 years	38	76.4	62.2–85.9	124	62.2	55.1–68.5	8	24.2	11.4–39.6	3	18.8	04.6–40.3	5	20.8	10.2–43.1
5 years	35	72.4	57.9–82.6	95	54.2	47.0–60.9	6	18.2	07.4–32.8	1	*	*	1	*	*
10 years	13	59.6	43.7–72.4	38	47.0	39.4–54.2	3	18.2	07.4–32.8	1	*	*	1	*	*
15 years	3	51.1	30.2–68.6	7	42.6	33.5–51.3	0	*	*	0	*	*	1	*	*

Table G- 41. Results of Univariate Analyses for Pre-Operative Variables

Variable	HR	*P* value	95% CI
Duration of epilepsy (range 1.6–51.4; IQR 12.0–25.4)			
≤18.5 years n = 151	Reference		
>18.5 years n = 150	1.5	0.01	1.09–2.03
Age at surgery (range 6.7–58.8; IQR 21.3–37.9)			
≤29.5 years n = 154	Reference		
>29.5 years n = 147	1.38	0.04	1.01–1.87
Age at onset (range 0.25–40; IQR 3–16)			
≤8 years n = 151	Reference		
>8 years n = 150	1.08	0.64	0.79–1.46
Preoperative secondarily generalized seizures			
None n = 147	Reference		
Previous n = 14	1.22	0.62	0.56–2.67
Occasional n = 75	1.60	0.01	1.11–2.34
Frequent n = 65	1.96	0.00	1.34–2.86

Table G-42. Cox Regression Analysis of Seizure Freedom According to "Beast Evidence" Pathology and Presence of Preoperative Generalized Seizures

Variable	HR*	SE	*P* value	95% CI
'Best evidence' pathology				
HS n = 201	Reference			
FTL n = 51	0.71	0.18	0.18	0.44–1.17
'Normal' n = 33	3.18	0.71	0.00	2.06–4.93
'Other' n = 16	3.11	0.90	0.00	1.76–5.48
Preoperative secondarily generalized seizures				
Absent/previous n = 161	Reference			
Occasional n = 75	1.60	0.30	0.01	1.11–2.32
Frequent n = 65	2.03	0.39	0.00	1.39–2.97

Log partial likelihood ratio test P = 0.0000. *HR after adjustment for the other variable in the model.

Table G-43. Probabilities of Seizure Freedom (95% CI) for Patients who are 1 or 2 Years Seizure Free After Surgery

Years post-surgery	Patients 1 year seizure free after surgery $n = 188$	Patients 2 years seizure free after surgery $n = 178$
1 year	100	100
2 years	92.5 (87.7–95.5)	100
5 years	81.5 (75.0–86.4)	86.1 (80.0–90.5)
10 years	70.3 (62.3–76.9)	74.4 (66.4–80.8)
15 years	62.6 (51.0–72.2)	66.6 (54.8–76.1)

Table G-44. Univariate Cox Regression for late Seizure Recurrence According to Duration of Preoperative Epilepsy, Age at Surgery, Age at Onset, and Presence of Preoperative Generalized Seizures

Variable	HR	*P* value	95% CI
Duration of epilepsy			
≤18.5 years $n = 96$	Reference		
>18.5 years $n = 74$	1.4	0.27	0.75–2.72
Age at surgery			
≤29.5 years $n = 98$	Reference		
>29.5 years $n = 72$	1.0	0.99	0.52–1.91
Age at onset			
≤8 years $n = 89$	Reference		
>8 years $n = 81$	1.0	0.99	0.53–1.88
Preoperative secondarily generalized seizures			
None/previous $n = 107$	Reference		
Occasional $n = 35$	1.04	0.93	0.46–2.33
Frequent $n = 28$	1.31	0.68	0.60–2.86

Table G-45. Anti-epileptic Drug Status and Seizure Recurrence Among Patients Seizure Free for Two Postoperative Years

Anti-epileptic drug status	Total	Seizure recurrence
Discontinued AEDs	83	13
Continued AEDs	74	24

Table G-46. Seizure-free probabilities for patients after Discontinuation of AEDs and for Patients who Remained on AEDs

Outcome after AEDs were discontinued ($n = 75$)			Outcome for patients seizure free >2 years and remained on AEDs ($n = 74$)		
Time after AEDs ceased	Probability seizure free (%)	95% CI	Time after 2 year postoperative anniversary	Probability seizure free (%)	95% CI
0.25 year	96.0	88.1–98.7	0.25 year	98.7	90.8–99.8
0.5 year	96.0	88.1–98.7	0.5 year	98.7	90.8–99.8
1 year	90.5	81.1–95.4	1 year	94.6	86.2–97.9
2 years	86.3	76.0–92.4	2 years	89.0	79.2–94.4
5 years	81.3	68.6–89.2	5 years	68.9	55.7–78.9

*The calculation of 'survival' for patients who discontinued AEDs commences at a later time than for patients who continued taking AEDs (i.e. AEDs were discontinued after 2 postoperative years). Data were reanalysed using the median time at which AEDs were discontinued (3.9 years post-surgery in this analysis) as a starting point for the analysis of patients who continued taking AEDs. There was no significant difference between groups ($P = 0.24$, $n = 137$); probabilities for those who discontinued AEDs differed no more than 3% from Table 7.

<table>
<tr><td colspan="8">Reference: Salanova V, Markand O, Worth R. Longitudinal follow-up in 145 patients with medically refractory temporal lobe epilepsy treated surgically between 1984 and 1995. Epilepsia 40(10):1417-1423 (1999).</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td></td></tr>
<tr><td></td><td></td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="7">The authors report the long-term longitudinal surgical outcome of 145 consecutive individuals with medically refractory temporal lobe epilepsy. The authors also correlated outcome with the clinical history, pathology, and the presurgical protocol in an attempt to identify those factors that are predictive of outcome.</td></tr>
<tr><td>Study Design</td><td colspan="7">Prospective Case Series</td></tr>
<tr><td rowspan="4">Population</td><td colspan="2">Inclusion Criteria</td><td colspan="5">Medically refractory temporal lobe epilepsy operated on by the same neurosurgeon between 1984 and 1995
Frequent disabling seizures several times a month for years, despite treatment with several AEDs</td></tr>
<tr><td colspan="2">Exclusion Criteria</td><td colspan="5">None Reported</td></tr>
<tr><td colspan="2">Study population Characteristics</td><td colspan="5">See Table G-47.
74 individuals had left-sided and 71 had right-sided resections.
The follow-up for 144 individuals ranged from 2 to 12 years (mean follow-up, 5.6 years). One individual died suddenly in the second year of follow-up. One individual was lost to follow-up 6 years after surgery.</td></tr>
<tr><td colspan="2">Generalizability to CMV drivers</td><td colspan="5">Unclear</td></tr>
<tr><td>Methods</td><td colspan="7">Individuals underwent a comprehensive presurgical evaluation, including neurological examination, visual field testing, psychometric testing, MRI of the head, prolonged video-EEG recordings with sphenoidal electrodes for 3-10 days, and interictal and ictal single-photon emission computed tomography (SPECT).
Follow-up was at 6 weeks, 3 months, 6 months, and then on a yearly basis. In addition the individuals were sent structured questionnaires each year on the anniversary of their surgery.
Engel's seizure outcome classification was used. According to Engel's classification, those individuals who had remained seizure free for ≥ 2 years were classified as class I.</td></tr>
<tr><td>Statistical Methods</td><td colspan="7">For statistical analysis, the authors applied the χ^2 test to compare the categoric data if the total number (n) was > 50. If the smallest expected value of any cell of the 2 x 2 contingency table was < 5, Yates' continuity correction was applied.
Longitudinal follow-up data of the seizure outcome after surgery were analyzed by actuarial analysis. Percentage of individuals achieving class I, II, III, and IV (Engel's seizure classification) outcome was determined at yearly intervals and plotted in a "life table" format to assess possible changes in the seizure outcome related to duration of follow-up after surgery. All the analysis was done on both the entire data set and a subset data set. The outcome variable of interest was class. The authors divided class into 2 groups (class 1 and 2 is one group, and class 3 and 4 is the other group) to fit the statistical analysis.
A repeated-measure ANOVA was used. Measurements were taken on each individual multiple times. Therefore a block diagonal covariance structure was used to account for the correlation between the multiple measurements on the same individual. The GEE was used to test whether there was any trend for class as time passes.
Three different trend test were used. First, the authors tested overall trend. Second, the authors fitted a piecewise linear regression, assuming a straight from year 1 to 6 (or 7) and then declining afterward. Third, the authors fitted another piecewise linear regression, assuming different linear relations before year 6 (or 7) and after.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Study quality=7.5</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td>NR</td><td>Y</td><td></td><td></td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="7">Seizure free
Remission rate</td></tr>
<tr><td>Results</td><td colspan="7">Sixty-six percent of the individuals were seizure free at 1-year follow-up, 63% at 2 years, and 60% had been seizure free for ≥ 2 years at 5-year follow-up. However, 68% became seizure free for ≥ 2 years at the time of last follow-up, and another 17% had rare seizures. Thus 85% were seizure free of had rare seizures with a mean follow-up period of 5.6 years. Of the 22 individuals with a follow-up of 10 years, 12 (55%) were seizure free from surgery to the time of last follow-up.
The longitudinal follow-up using actuarial analysis showed that follow-up at 1 and 2 years is highly predictive of the long-term outcome. There was some decline in the percentage of individuals in class I and II on long-term follow-up (see Figure 1). However, the outcome showed remarkable stability over several years after surgery. The percentage of individuals in class I and II remained stable for the years 1 – 6 of follow-up. After 7 years of follow-up, there was a slight negative trend, with a decrease in the percentage of individuals in class I and II; however, this was not statistically significant (p > 0.15).
Of the 96 individuals who were seizure free in the first postoperative year, 16 (17%) had recurrent seizures at the time of last follow-up; the probability of remaining seizure free was thus 83%. Only seven (8%) of the 91 individuals seizure free 2 years after surgery had recurrent seizures in later years (probability of remaining seizure free, 92%). The recurrence rate for those individuals seizure free for ≥ 2 years at 3 and 5 years of follow-up was 6 and 7%, respectively.</td></tr>
</table>

	Fifteen (31%) of the 49 individuals who continued to have seizures 1 year after the surgery eventually became and remained seizure free for ≥ 2 years at the time of last follow-up. The remission rate for individuals who continued to have seizures 2 and 3 years after surgery was 17 and 11%, respectively, and for those individuals who had seizures 4 and 5 years after surgery, the remission rate was 10 and 8%, respectively.
Authors' Comments	Actuarial analysis showed that the long-term surgical outcome of temporal lobe epilepsy remains favorable. Follow-up at 1 and 2 years is highly predictive of the long-term outcome.

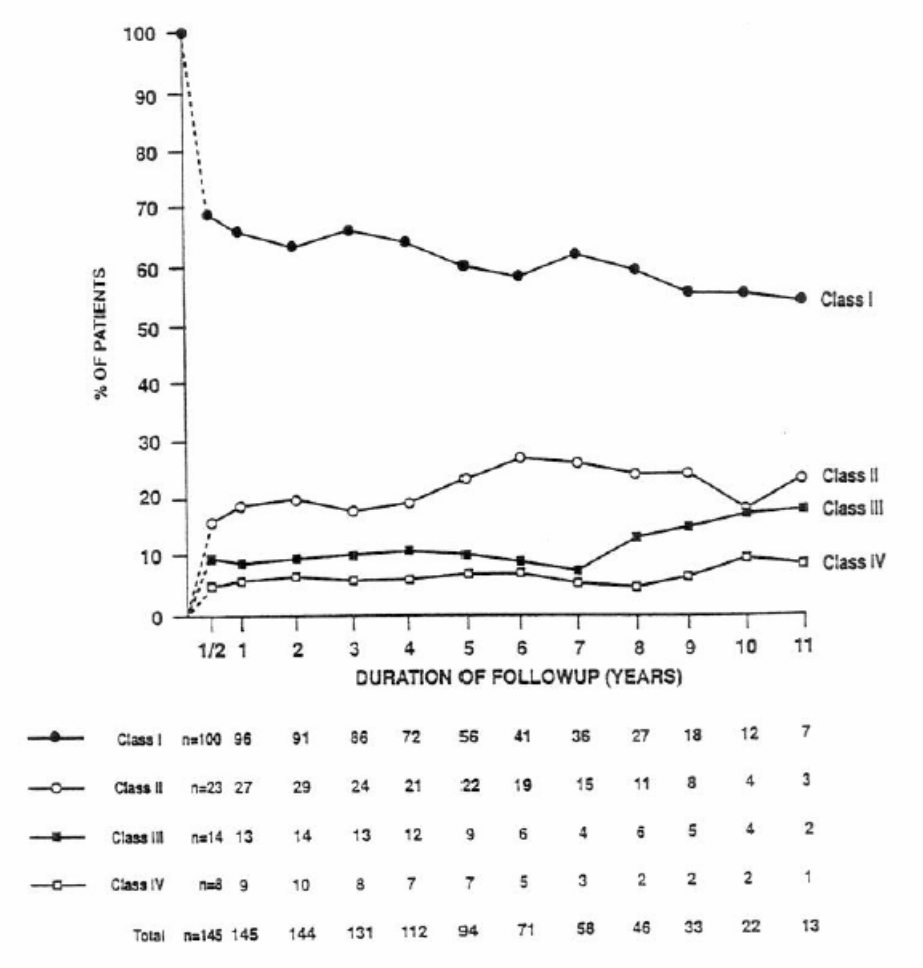
Table G-47. Patient Characteristics

Mean age of seizure onset	10.5 yr (range, 4 mo. to 39 yr)
Mean age at surgery	30.4 yr (range, 8–53 yr)
Mean duration of epilepsy	19.7 yr (range, 1–45 yr)
Febrile convulsion or febrile illness with seizures	62 (43%)
Head injury	13 (9%)
Small tumors	3 (2%)
Cavernous angiomas	8 (5.5%)
Arachnoid cyst	2 (1%)
Cortical dysplasia	8 (5.5%)
No etiology	49 (33.8%)
Abnormal MRI	77/138 (56%)
Abnormal ictal SPECT	87/106 (82%)
Ipsilateral FDG-PET hypometabolism	33/42 (78%)

MRI showed mesial temporal sclerosis in 46%. MRI volumetric analysis became available in 1994. Ictal SPECT showed increased flow on the side of ictal onset. PET scan became available in 1993.

MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; PET, positron emission tomography.

Figure G-5. Percentage of Patients in Each Outcome Category During Each Year of Followup (Class I are Seizure Free Patients)



<table>
<tr><td colspan="15">Reference: So EL, Radhakrishnan K, Silbert PL, Cascino GD, Sharbrough FW, O'Brien PC. Assessing changes over time in temporal lobectomy: outcome by scoring seizure frequency. Epilepsy Research 27:119-125 (1997).</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="2">6</td><td colspan="2"></td></tr>
<tr><td></td><td colspan="2"></td><td colspan="2">X</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="14">The aim of this study was to assess the practicality of using the Seizure Frequency Scoring System in determining the pattern of long-term postoperative course in a cohort of individuals who underwent anterior temporal lobectomy (ATL) for intractable epilepsy.</td></tr>
<tr><td>Study Design</td><td colspan="14">Prospective Case Series</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Individuals underwent first-time ATL with amygdalohippocampectomy for control of medically intractable complex partial epilepsy.
Individuals who had at least 1 year of postoperative follow-up were included.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">Individuals with extratemporal surgery were not included.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">See Table G-48</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">One hundred and ninety individuals underwent first-time ATL with amygdalohippocampectomy for control of medically intractable complex partial epilepsy. The cohort in this study comprised 184 consecutive individuals who had at least 1 year postoperative follow-up. All individuals underwent the same technique for resection of the lateral temporal cortex and the mesial temporal structures, which included the amygdala, the hippocampus and the parahippocampal gyrus.
Charts were reviewed to collect information on demographics, epilepsy history and postoperative seizure frequency. Routine postoperative follow-up visits were scheduled at 1 week, 3 months, 1 year and each year thereafter. Table G-49 shows the system for scoring seizure frequency. Seizure control was considered excellent in those with scores of 0 – 4, since they did not have disabling seizures.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Comparisons between adjacent time points were made for the overall seizure frequency scores and for the proportion of individuals with excellent outcome. Only individuals with follow-up for both time points were included for statistical testing. Paired t-tests were used for overall seizure frequency scores and sign tests were used for excellence of outcome. These analyses were also performed on sub-cohorts of patients who had the same number of years of follow-up.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Study quality=5.2</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>NR</td><td>Y</td><td>Y</td><td>N</td><td>N</td><td>N</td><td>NR</td><td>NR</td><td>Y</td><td></td><td></td></tr>
<tr><td rowspan="2">Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Seizure frequency score</td></tr>
<tr><td>Results</td><td colspan="14">Table G-50 shows the distribution of individuals by seizure frequency score and by year of follow-up. The only statistically significant change in seizure frequency scores during follow-up was between the third and the fourth years (2.61 and 2.11; p = 0.045).
The proportion of individuals with excellent outcome was determined for each postsurgical year of follow-up (i.e., seizure frequency scores 0 – 4; Table G-51). There was no statistically significant difference between successive years in the proportion with excellent outcome.
The authors also determined whether outcome remained unchanged when follow-up at each year was confined to the same individuals throughout their postsurgical course. The 184 individuals were divided into a subgroup of individuals with total duration of follow-up of 2 years (n = 47), a subgroup with 3-year follow-up (n = 61), a subgroup with 4-year follow-up (n = 39), and a subgroup with 5-year follow-up (n = 32). In every subgroup, there was no statistically significant difference between adjacent time points in the rate of achieving excellent outcome (p > 0.05; Figure G-6). In those with 5 years of postsurgical follow-up, the seizure frequency score also remained unchanged throughout follow-up (p > 0.05; Table G-52).</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">By using the Seizure Frequency Scoring System, the authors have demonstrated that seizure outcome remains stable after ATL. The scoring system facilitates the detection of subtle changes in the postoperative course.</td></tr>
</table>

Table G-48. Patient Characteristics

	%	Median	Range
Male	45.3		
Female	54.7		
Handedness			
Right	85.8		
Left	11.6		
Ambidextrous	2.6		
Age at first unprovoked seizure (year)		8	162
Age at surgery (year)		31	786
Duration of epilepsy before surgery (year)		19.5	<181
Duration of follow-up (year)		3.4	1.1–5.7
Epilepsy types according to cause			
Symptomatic	61.1		
Cryptogenic	38.9		

Table G-49. Seizure Frequency Scoring System

Seizure frequency	Score
Seizure-free, off antiepileptic drug	0
Seizure-free, need for antiepileptic drug unknown	1
Seizure-free, requires antiepileptic drugs to remain so	2
Nondisabling simple partial seizures	3
Nondisabling nocturnal seizures only	4
1–3 per year	5
4–11 per year	6
1–3 per month	7
1–6 per week	8
1–3 per day	9
4–10 per day	10
>10 per day but not status epilepticus	11
Status epilepticus without barbiturate coma	12

Table G-50. Distribution of Patients by Seizure Frequency Score and by Year

Seizure frequency score	Year 1 ($n = 184$)		Year 2 ($n = 179$)		Year 3 ($n = 132$)		Year 4 ($n = 71$)		Year 5 ($n = 32$)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
0	2	1.1	3	1.7	12	9.1	16	22.5	7	21.9
1	99	53.8	102	57.0	68	51.5	31	43.7	11	34.4
2	18	9.8	14	7.8	6	4.5	2	2.8	1	3.1
3	17	9.2	14	7.8	9	6.8	7	9.9	3	9.4
4	8	4.3	5	2.8	3	2.3	2	2.8	1	3.1
5	14	7.6	12	6.7	9	6.8	3	4.2	1	3.1
6	10	5.4	9	5.0	8	6.1	2	2.8	3	9.4
7	6	3.3	11	6.1	8	6.1	5	7.0	2	6.3
8	8	4.3	6	3.4	6	4.5	3	4.2	3	9.4
9	0	0.0	1	0.6	1	0.8	0	0.0	0	0.0
10	1	0.5	2	1.1	2	1.5	0	0.0	0	0.0
11	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0
12	0	0	0	0	0	0	0	0	0	0
Mean seizure score	2.5815		2.5698		2.6136		2.1127		2.7188	

Table G-51. Patients with Excellent Outcome at each Postsurgical Year of Followup

Seizure frequency score	Year 1 ($n = 184$)		Year 2 ($n = 179$)		Year 3 ($n = 132$)		Year 4 ($n = 71$)		Year 5 ($n = 32$)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Excellent outcome	144	78.3	138	77.1	98	74.2	58	81.7	23	71.9

Figure G-6. Proportion of Patients with Excellent Outcome at Each Year of Followup for Each Group of Patients with the same Duration of Followup

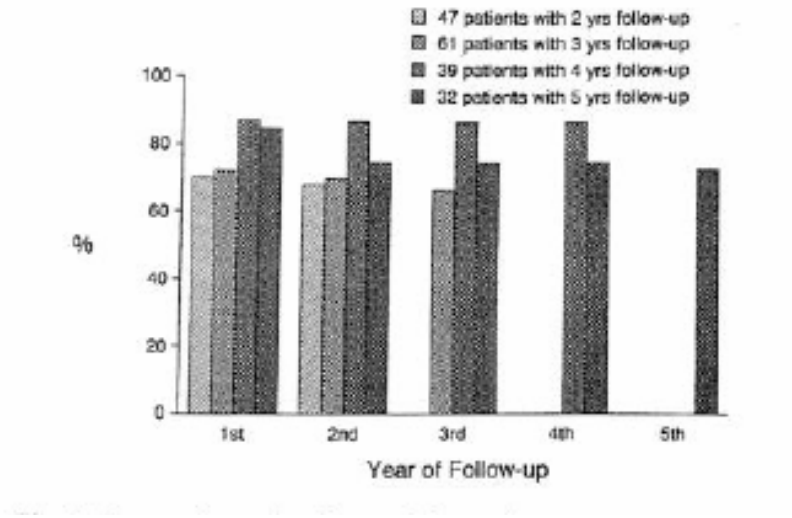


Table G-52. Distribution by Seizure Frequency Score and by Year of Followup of 32 Patients with Five Years of Followup

Seizure frequency score	Year 1		Year 2		Year 3		Year 4		Year 5	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
0	0	0.0	0	0.0	3	9.4	6	18.8	7	21.9
1	17	53.1	17	53.1	16	50.0	12	37.5	11	34.4
2	3	9.4	3	9.4	1	3.1	2	6.3	1	3.1
3	5	15.6	3	9.4	3	9.4	3	9.4	3	9.4
4	2	6.3	1	3.1	1	3.1	1	3.1	1	3.1
5	2	6.3	3	9.4	2	6.3	1	3.1	1	3.1
6	1	3.1	2	6.3	1	3.1	2	6.3	3	9.4
7	1	3.1	2	6.3	3	9.4	3	9.4	2	6.3
8	1	3.1	1	3.1	2	6.3	2	6.3	3	9.4
9	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0
Mean seizure score	2.4063		2.6563		2.6250		2.5938		2.7188	

<table>
<tr><td colspan="14">Reference: Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, Shinnar S, Langfitt JT, Walczak TS, Pacia SV. Predicting long-term seizure outcome after resective epilepsy surgery: The Multicenter Study. Neurology 65:912-8 (2005).</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td>3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="2">6</td><td colspan="2"></td><td></td></tr>
<tr><td></td><td colspan="2"></td><td>X</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td></td></tr>
<tr><td>Research Question</td><td colspan="13">The authors examined probability and predictors of entering 2-year remission and the risk of subsequent relapse.</td></tr>
<tr><td>Study Design</td><td colspan="13">Prospective Case Series</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="12">Eligible study subjects had localization-related epilepsy and were evaluated for resective surgery between 1996 and 2001. They were over 12 years of age at presentation, had failed at least two first-line antiepileptic drugs, and had at least one seizure per month, by history.
Patients were required to have had resective surgery and be followed at least 2 years postoperatively.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="12">None reported</td></tr>
<tr><td>Study population Characteristics</td><td colspan="12">Of 396 patients who underwent resective surgery in the multicenter cohort, 339 (86%) were followed for at least 2 years after surgery. Of these 339 patients, 297 had mesial temporal lobe resections and 42 had resections in neocortical regions. In these 339 patients, median follow-up is 4.6 years (range 2 to 7.3 years). Patient characteristics were reported for the original 396 patients who underwent resective surgery, however the characteristics for the 339 patients who were followed for at least 2 years following surgery were not reported. As a result, we are not able to report the characteristics of the study population.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="12">Unclear</td></tr>
<tr><td>Methods</td><td colspan="13">The study was a seven-center prospective design for which patients were recruited at their initial referral visit for surgical evaluation. A standardized protocol for patient evaluation, selection, and surgical approach was used at all seven sites.
Information on preoperative historical factors was obtained from medical record review and from patient interview at baseline. Postsurgically, patients were called every 3 months to ascertain seizure frequency. Medication withdrawal in seizure-free patients followed usual practice at each center, and was considered by agreement only in patients with at least 2-year remission after informed patient decision.
To be included in the following analyses of seizure remission and relapse, patients were required to have had resective surgery and be followed at least 2 years postoperatively. The authors defined seizure remission as 2 years completely seizure free, with or without isolated auras, and they defined relapse as the occurrence of any seizure after attaining 2-year remission, regardless of any ascribed cause. Remission was counted from the day of discharge from the hospital.
The initial analysis considered whether type of surgery (mesial temporal resection vs resection in any neocortical region including temporal lobe) was associated with remission or relapse after remission. For analyses of predictors of seizure remission and relapse, the authors focused on presurgical information. They considered numerous seizure variables (classification, frequency, severity); chronologic variables (duration and age at onset of epilepsy; age at study entry); and demographic variables (sex, race, cognitive function, education, employment). Other variables were related to results and localization of preoperative evaluation procedures (MRI with focal abnormal features, and unilateral or bilateral hippocampal atrophy on qualitative interpretation, with or without signal change; ictal and interictal EEG localization from scalp and intracranial recordings; neuropsychological assessment; neurologic examination) and their unilaterality/bilaterality/relationship to one another. The authors also considered a few postoperative variables including the results of the pathology report, the interval to seizure remission counted from day of hospital discharge, and the presence of auras in postoperative seizure-free patients.</td></tr>
<tr><td>Statistical Methods</td><td colspan="13">Bivariate analyses were performed with χ^2 tests and tests for trend when appropriate. In addition, proportional hazards analysis was used to estimate bivariate rate ratios (RR) for each factor with respect to both of the outcomes, 2-year remission and relapse after 2-year remission. The authors calculated 95% CIs. Certain key findings are also displayed as Kaplan Meier curves. For multivariate analysis, the authors used a proportional hazards model.</td></tr>
<tr><td rowspan="3">Quality assessment</td><td rowspan="2">Study quality = 8.2</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td></td><td></td></tr>
<tr><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>No</td><td>No</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td></td><td></td></tr>
<tr><td>High</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="13">Two year remission.
Relapse after 2-year remission.</td></tr>
<tr><td>Results</td><td colspan="13">Two year remission. A total of 223 patients experienced at least a 2-year remission from seizures postoperatively. The cumulative probability of 2-year remission at 2, 3, 4, and 5 years after surgery was 0.46 (95% CI = 0.41, 0.52), 0.60 (0.55, 0.66), 0.66 (0.60, 0.71), and 0.69 (0.63, 0.74). In the medial temporal group, 202 (68%) of the 297 remitted (34 of whom had continued auras), vs 21 (50%) of the 42 in the neocortical group (p = 0.02). When variation in follow-up was taken into account in a proportional hazards model, this difference did not attain significance, RR = 1.46 (0.93, 2.28), p = 0.10 (Figure G-7).
Of all the variables considered, only absence of a history of generalized tonic clonic seizures (GTC) (with the exception of those associated with drug withdrawal in hospital or on initial presentation of epilepsy) and the presence of hippocampal atrophy (HA) on the presurgical MRI were significantly associated with attaining remission. Several other variables such as a history of febrile seizures and age at onset were marginally significant. Remission rate showed a gradual but not significant decrease with increasing</td></tr>
</table>

	age at surgery. In a multivariate proportional hazards model, a history of GTCs (RR = 0.65, CI = 0.46, 0.91, p = 0.01) and HA (RR = 1.58, CI = 1.13, 2.21, p = 0.007) was independently associated with remission. No other variables, including a history of febrile seizures, approached significance. Although the authors did examine potential predictors of remission in the group with neocortical resections, no factor was found to be significant. **Relapse after 2-year remission.** Following entry into a 2-year remission, patients in this cohort have been followed a median of 2.4 years (range 0 to 5.1 years). Of the 223 patients who entered a 2-year remission, 55 (25%) have subsequently relapsed. The risk of relapse at 1, 2, and 3 years after entering remission was 0.13 (0.08, 0.18), 0.23 (0.17, 0.29), and 0.30 (0.23, 0.38). There was no discernible difference in relapse risk between mesial temporal (51/202, 25%) and other resections (4/21, 19%). The rate ratio for neocortical vs medial temporal resection was 1.45 (0.53, 4.02), p = 0.47 (Figure G-8). The authors examined a series of factors as potential predictors of relapse within the mesial temporal resection group. Of all the factors examined, none was significantly associated with the risk of a relapse after 2-year remission. In this group, 32% (11/34) of patients with continued auras relapsed compared to 24% (40/168) of those without auras (p = 0.30). In a proportional hazards model, the rate ratio for having continued auras is 1.54 (0.79, 3.03), p = 0.20. While some relapses occurred in temporal proximity to reduction of medication, the reduction of AEDs was not associated with increased risk of relapse in this cohort. The only factor found to be predictive of relapse, and only in the mesial temporal lobe group, was whether remission occurred immediately after hospital discharge or whether it was delayed (the patient had one or more seizures after hospital discharge before attaining remission). A total of 33 of 142 (23%) of those who immediately remitted had relapse, compared with 18/60 (30%) of those with delayed remission. While the difference between these simple proportions is not significant (p = 0.31), once length of follow-up is taken into account, the difference between these groups is substantial, RR = 0.50 for immediate remission (95% CI = 0.28, 0.89), p = 0.02 (Figure G-9). In the group with neocortical resections, there were only four relapses. None of the factors the authors examined as potential predictors of seizure outcome was associated with relapse in this group.
Authors' Comments	There was an excellent seizure response to resective epilepsy surgery. Two-year remission was achieved in 68% of the patients who had medial temporal lobe resections, vs 50% of those who had neocortical resections. Unlike what has been reported in other studies, after adjusting for length of follow-up, the difference in remission response in medial temporal vs neocortical resections was not statistically significant. While the authors did not find a significant difference in remission rates between medial temporal and neocortical resection groups, the number of neocortical surgery patients was too small to have the power to detect moderate differences between these groups, and the authors could not rule out a two and a half fold difference in those remission rates. Over 30% of patients do not achieve remission, and 25% of resected patients relapse after achieving a 2-year remission, a rate also not found to be significantly different between the medial temporal and neocortical resected groups in our population. This observation is also at odds with some but not all prior reports, which mostly suggested a higher relapse rate (at least after 1 year of seizure freedom) in mesial temporal vs neocortical resected patients. Although the estimate of effect suggests little difference in relapse after remission in medial temporal vs neocortical resected patients, the authors could not rule out a substantially higher risk in the medial temporal group, or a relative doubling of the risk in the neocortical group, because of the small number of neocortical resections. Despite the large number of contemporary patients in this analysis, followed prospectively with extensive data from pre- and postoperative interventions, and careful determination of seizure outcome with frequent patient contact, prediction of remission and relapse is still elusive. Only the absence of a history of generalized tonic clonic seizures and the presence of hippocampal atrophy preoperatively predicted remission in mesial temporal resected patients. These two findings were anticipated, based on other analyses. But numerous other isolated factors mentioned in prior reports were not substantiated as predictors of seizure remission. The addition of more patients, more factors, and more follow-up only diminished the independent predictors of seizure outcome. Most prior reports did not investigate predictors of relapse, or found none. The authors found only one factor to be a significant predictor of relapse, namely the postoperative latency to remission. Patients who had no further seizures after hospital discharge (entered immediate remission) were less likely to relapse than those who entered remission later (i.e., had any seizures after discharge). Although the authors did not find significant differences in remission or relapse rates in patients with different seizure frequency, age at onset, or duration of epilepsy, remission rate showed a gradual, consistent decrease with increasing age at surgery. In the absence of any data to suggest that this difference relates to longer history, or a greater lifetime seizure burden, and thereby implicates an hypothesis like kindling, one could speculate that operative factors or risks, AED exposure (specific, cumulative amount), independent age-related medications, or age dependent etiology might play a role. This association, however, failed to reach significance in their large sample.

Figure G-7. Cumulative probability of Remission by Resection Site

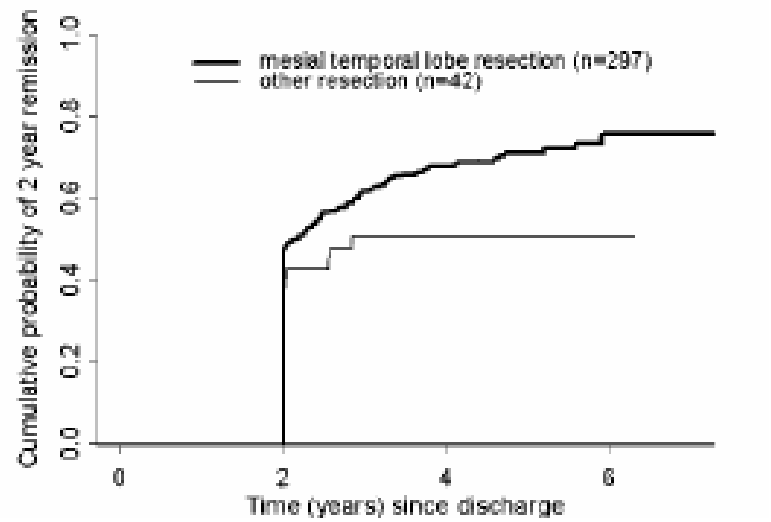


Figure G-8. Cumulative Probability of Relapse by Resection Site

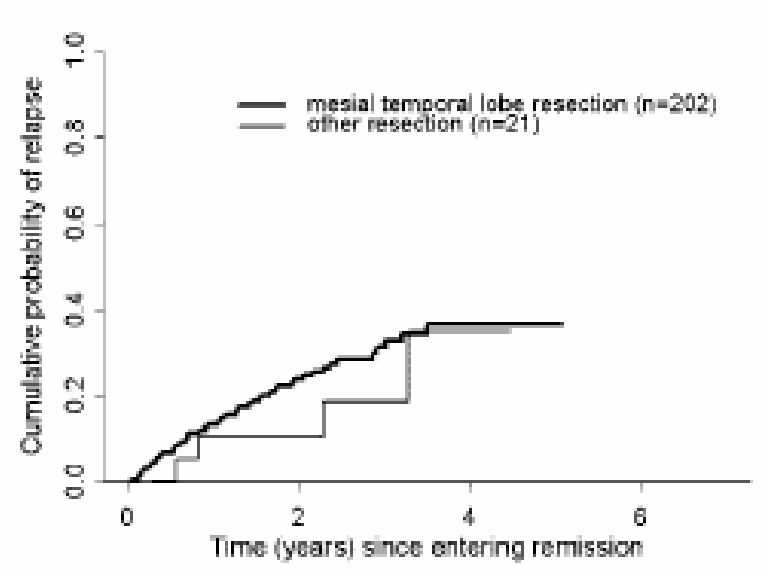
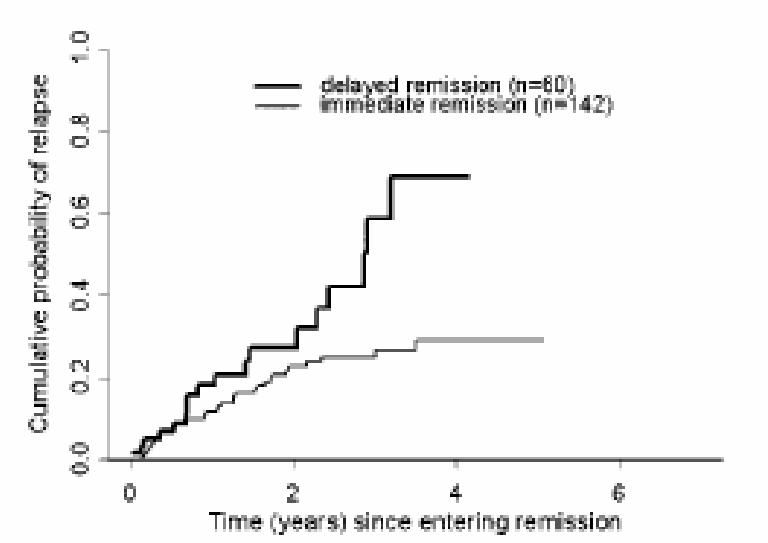


Figure G-9. Cumulative Probability of Relapse, by time of Remission, in Patients with Medial Temporal Resections



Reference: Yoon HH, kwon HL, Mattson RH, Spencer DD, Spencer SS. Neurology 2003;61:445-450														
Key Questions Addressed	1	2	3	4	5	6								
			X											
Research Question	To evaluate the likelihood of and risk factors for seizure recurrence in patients initially seizure-free after resective surgery for intractable epilepsy.													
Study Design	Retrospective Case Series													
Population	**Inclusion criteria**	(1). Patients who remained seizure-free in the first postoperative year and who had at least 3 years' follow-up (2). Patients who had seizures during postoperative hospitalization												
	Exclusion criteria	(1). Patients who underwent callosotomy or hemispherectomy												
	Study population characteristics	The study group comprised of 175 patients (see Table G-53)												
	Generalizability to CMV drivers	Unclear												
Methods	One hundred seventy-five patients who underwent lobectomy between 1972 and 1992 and were seizure-free during the first postoperative year were retrospectively studied.													
Statistical Methods	The t-test was used to analyze continuous variables and the X^2 test was used to examine categorical variables. Kaplan-Meier plots were used to account for varying lengths of follow-up and unadjusted curves were compared using the log-rank test. The Cox proportional hazards models were used to examine the effect of variables that affected Kaplan-Meier analysis ($p < 0.05$) as well as variables considered potentially predictive a priori. Hazard ratios from Cox models were presented with 95% confidence interval and probability values were two sided. Outcomes were evaluated based on the presence of auras in otherwise seizure-free patients. Logistic regression was used for variables that were significant ($p < 0.05$) in bivariate analysis and considered potentially predictive a priori.													
Quality assessment	Study quality=6.4	1	2	3	4	5	6	7	8	9	10	11	12	13
		N	Y	Y	N	Y	N	N	Y	Y	Y	Y		
	Moderate	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	(1). Relapse risk (2). Presence of auras in otherwise seizure-free patients (3). Seizure frequency among relapsers													
Results	Of the 175 patients (mean follow-up 8.4 years), 63% never relapsed. The likelihood of being seizure-free was 83 $\pm$ 6% 3 years after surgery, 72 $\pm$ 7% after 5 years, and 56 $\pm$ 9% after 10 years. Bivariate analysis (see Table G-54) revealed that patients with tumors were less likely to have auras than those without tumors and those with mesial temporal sclerosis were morel likely to have auras than those without. Among patient who relapsed, the interval until first recurrence did not predict whether a patient would have a mild vs. moderate recurrence, that is, one or less, or more than one seizure per year (see Table G-55). Logistic regression was used to examine the association between aura risk and potential predictive factors. Duration or preoperative epilepsy remained significantly associated with increased aura risk after adjusting for pathology, temporal vs. extratemporal location, and age at surgery (see Table G-56).													
Authors' Comments	In patients seizure-free during the first year after resective epilepsy surgery, the likelihood of remaining seizure-free declined to 56%, but half of the patients who relapsed had at most one seizure per year. Longer preoperative illness and normal pathology predicted poorer outcome.													
Reviewers' Comments	Subjective data was obtained by telephone interviews in cases where follow-up within the last year was unavailable in the charts.													

Table G-53. Patient Characteristics

Characteristics	n (%)*	Median	Range
Gender			
Male	91 (52)		
Side of surgery			
Right	78 (45)		
Lobe resected			
Temporal only	140 (80)		
Temporal plus†	7 (4)		
Frontal only	12 (7)		
Frontal plus‡	1 (0.6)		
Parietal only	5 (3)		
Parietal plus§	3 (2)		
Occipital only	7 (4)		
Age at surgery, y		27.6	3.1–54.7
3–12	2 (1)		
13–19	34 (19)		
20–29	67 (39)		
≥30	71 (41)		
DPE, y		16.3	0.18–44.3
<20	108 (64)		
20–30	42 (25)		
>30	20 (12)		
Pathology			
MTS‖	78 (45)		
Tumor	44 (25)		
Developmental	16 (9)		
Vascular	6 (3)		
Normal	22 (13)		
Other¶	7 (4)		
Follow-up duration, y		8.0	3.1–20.0

* Percentages may not always sum to 100 because of rounding.
† Three resections included the occipital lobe, two the parietal, and two both the parietal and the occipital.
‡ This resection included the parietal lobe.
§ All resections included the occipital lobe.
‖ Includes five patients with a second lesion: four developmental and one with an unspecified cyst.
¶ Includes two cases of apparent trauma, two cases of perivascular infiltrates thought to represent viral encephalitis, and one case each of cysticercosis, encephalolith, and sclerosing angiomatous proliferation.

DPE = duration of preoperative epilepsy; MTS = mesial temporal sclerosis.

Table G-54. Bivariate Analysis of Factors Associated with Postoperative Outcome

Factors	Relapsers, % (n)*	*p* value	Seizures/y >1, % (n)†	*p* value	Auras, % (n)‡	*p* value
Gender						
Male	34 (31)	0.35	52 (15)	0.72	28 (17)	0.20
Female	40 (34)		47 (16)		18 (9)	
Side of resection						
Right	37 (29)	0.99	45 (13)	0.51	16 (8)	0.11
Left	37 (36)		53 (18)		30 (18)	
Lobe						
Pure temporal	38 (53)	0.70	48 (25)	0.69	28 (24)	0.058
Extratemporal§	34 (12)		55 (6)		9 (2)	
Pathology						
MTS	38 (30)	0.83	47 (16)	0.72	38 (18)	0.0026
Non-MTS	37 (35)		52 (15)		13 (8)	
Normal	55 (12)	0.051	75 (9)	0.047	20 (2)	0.76
Abnormal	35 (53)		43 (22)		24 (24)	
Tumor	30 (13)	0.21	38 (5)	0.38	6 (2)	0.0079
Nontumor	40 (52)		52 (26)		30 (24)	
Age at surgery, y						
≥30	46 (33)	0.027	50 (16)	0.80	26 (10)	0.63
<30	30 (31)		47 (14)		22 (16)	
DPE, y						
≥20	53 (33)	0.00058	48 (16)	0.80	45 (13)	0.0023
<20	27 (29)		52 (14)		16 (13)	
Age at epilepsy onset, y						
≥10	36 (31)	1.0	40 (12)	0.12	19 (10)	0.18
<10	36 (31)		60 (18)		30 (16)	

* Among all patients (n = 175), those who relapsed at any point after surgery.
† Among relapsers (n = 63), those who experienced more than one seizure per year following first relapse.
‡ Among patients who never relapsed (n = 110), those who experienced auras at any point after surgery.
§ Includes seven patients with multilobe resections involving the temporal lobe.

MTS = mesial temporal sclerosis; DPE = duration of preoperative epilepsy.

Table G-55. Outcome of Late vs. Early Relapsers

	Severe recurrence		Moderate recurrence	
Time to relapse, y	Seizures/mo > 1, % (n)	*p* value	Seizures/y > 1, % (n)	*p* value
≥5 (late relapse)	0 (0)	0.087	47 (8)	0.82
<5	22 (10)		50 (23)	
≥2	13 (6)	0.31	46 (21)	0.36
<2 (early relapse)	24 (4)		59 (10)	

Seizures/mo = no. of seizures per month following first relapse; Seizures/y = no. of seizures per year following first relapse.

Table G-56. Multivariate Models for Predictors of Seizure Outcome after Surgery

	Results of Cox proportional hazards model examining relation of potential predictors to risk of relapse, n = 175			Results of logistic regression model examining relation of potential predictors to risk of auras* when otherwise seizure-free, n = 110		
Predictors	HR†	95% CI	*p* value	OR†	95% CI	*p* value
Age at surgery ≥30 y	1.61	0.89, 2.93	0.12	0.71	0.22, 2.33	0.57
DPE ≥20 y	1.76	0.96, 3.22	0.069	3.55	1.06, 11.90	0.040
Pathology‡						
MTS	1.21	0.61, 2.40	0.58	2.95	0.85, 10.25	0.089
Normal	2.38	1.06, 5.34	0.036	1.49	0.22, 10.27	0.69
Pure temporal lobe§	0.84	0.35, 2.01	0.69	1.14	0.18, 7.33	0.89

* Presence or absence of auras at any point in follow-up among 110 otherwise seizure-free patients.
† Simultaneously adjusted for all other variables in the model.
‡ Reference for each pathology group is a category combining tumor, developmental, vascular, and other.
§ Reference is the extratemporal group, which includes seven patients with multilobe resections involving the temporal lobe.

HR = hazard ratio; OR = odds ratio; DPE = duration of preoperative epilepsy; MTS = mesial temporal sclerosis.

Study Summary Tables for Key Question 4

Reference: Gilad R, Lampl Y, Gabbay U, Eshel Y, Sarova-Pinhas I. Early Treatment of a Single Generalized Tonic-Clonic Seizure to Prevent Recurrence. Arch Nerol/Vol 53: 1996:1149-1152.

Key Questions Addressed	1	2	3	4	5	6
				√		

Research Question	• To determine the rate of recurrence of a second seizure after a single unprovoked epileptic seizure. • To establish a treatment policy for patients.	
Study Design	Prospective Controlled Trial	
Population	**Inclusion Criteria**	• Patients seen in outpatient clinic between 1985 and 1990, whom experienced a single epileptic attack of the generalized tonic-clonic type and seen at a hospital within the first 24 hours after the unprovoked attack.
	Exclusion Criteria	Patients with: • Partial seizure or history of partial seizures • Seizure induced by alcohol or other drugs or toxic substances; including metabolic disorder • Status epilepticus • Progressive neurological disease • New or old infarction of the brain • Intracerebral bleeding • Brain tumors • Vascular malformations confirmed by in medical history or neurological imaging.
	Study population Characteristics	**N=87 total patients** 45 patients treated 42 patients untreated **Age**: 18 to 50 years See Table G-57.
	Generalizability to CMV drivers	Unclear
Methods	• Detailed family history evaluated for each patient. • 87 patients with a single generalized tonic-clonic seizure randomly divided into 2 groups (45 patients receiving anticonvulsive treatment and 42 who remained untreated for a follow up period. • The endpoint of the study was 36 months after single attack or the occurrence of subsequent epileptic attack. • All patients examined by 3 neurologists specializing in epileptology. • Biochemical analysis, echocardiography, cardiac monitoring, electroencephalography (EEG), and neuroimaging of the brain were performed on each patient. • Patients in the treated group given monotherapy with carbamazepine as first drug of choice; treatment with valproic acid given to patients experiencing side effects. • Serum drug intervals measured every 3 months and maintained with therapeutic range of 1751µmol/L); valproic acid target reference range 350 to 700µmol/L. • Patients followed once monthly for 36 months or until occurrence of second seizure.	
Statistical Methods	• Results of recurrence analyzed using the product-limit estimate, a method under Kaplan-Meier. • *P*-value of .05 or less considered statistically significant. • To compare the survival curves of the treated and control groups, the log rank test was used.	

Quality assessment														
	Quality Score = 8.3	1	2	3	4	5	6	7	8	9	10	11	12	13
		Y	Y	Y	NR	Y	Y	Y	NR	Y				
	Moderate	14	15	16	17	18	19	20	21	22	23	24	25	

Relevant Outcomes Assessed	Risk in seizure recurrence.
Results	• In all patients, the recurrent seizures were of the generalized tonic-clonic type. • Second epileptic attack occurred in:

	○ 29 patients (71%) of the untreated group ○ 10 patients (22%) of the treated group • Results indicate a significantly higher percentage of seizure-free patients in the treated group compared with that of untreated group (*P*=.001). • Treated men risks appeared lower for recurrence compared with treated women (*P*<.001 vs *P*=.03, respectively). • Compare: ○ Figure G-10. Survival function estimates for men in the treated (squares) and untreated (circles) groups. ○ Figure G-11. Survival function estimates for women in treated (squares) and untreated (circles) groups
Authors' Comments	• Treatments after a single provoked seizures leads to significantly reduced generalized tonic-clonic epilepsy relapse risks.

Table G-57. Age and Sex Distribution and Percentage of Patients with a recurrent epileptic attack after 12, 24, and 36 months in the 2 study groups.

Characteristic and Follow-up	Treated Group (n=45)	Untreated Group (n=42)
Characteristic		
Age, y, mean±SD	30.12±1.3	32±2.5
Sex ratio, F/M	24/21	21/21
Follow-up, mo		
12	6 (13)	24 (59)
24	9 (20)	28 (68)
36	10 (22)	29 (71)

**Data for follow-up are given as the number (percentage) of patients.*

Figure G-10. Survival function estimates for men in the treated (squares) and untreated (circles) groups.

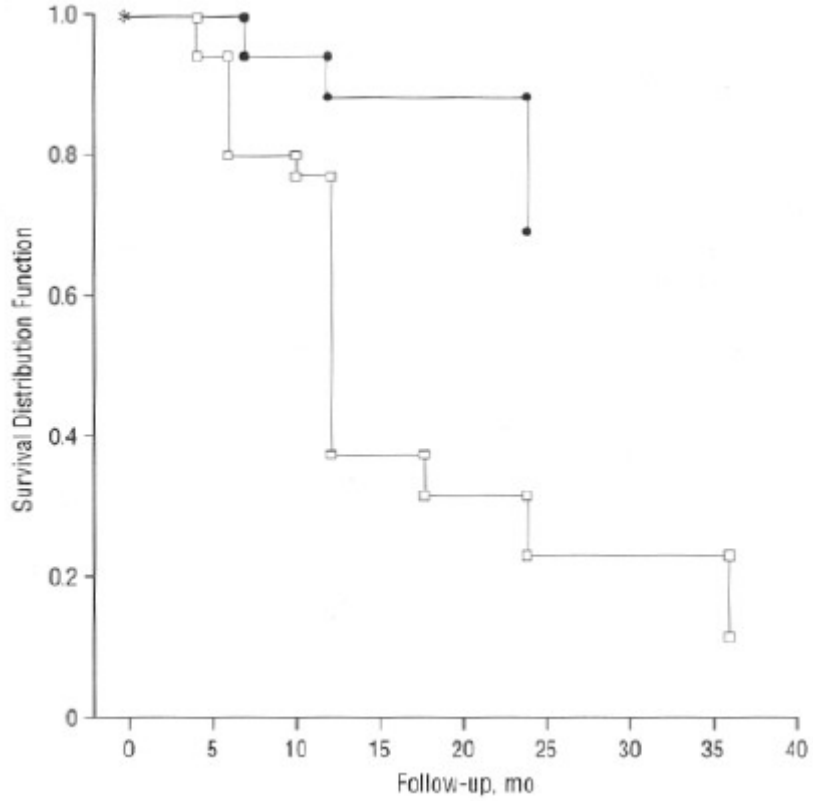
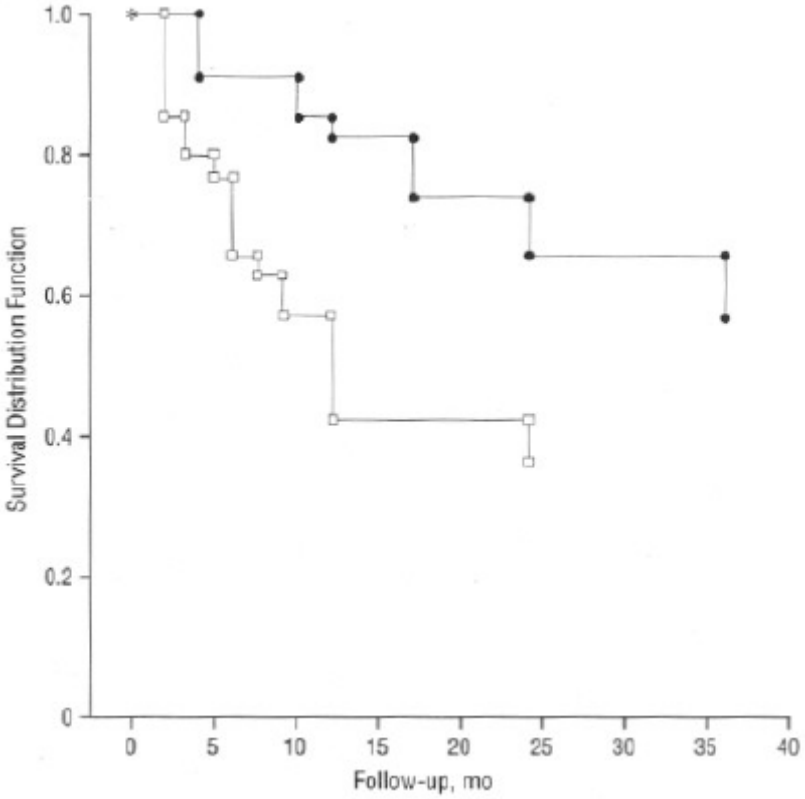


Figure G-11. Survival function estimates for women in treated (squares) and untreated (circles) groups



<table>
<tr><td colspan="15">Reference: Hopkins A, Garman A, Clarke C., The Lancet: The first seizure in adult life.1988: 721-726.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td colspan="2">1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="2">6</td></tr>
<tr><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2">√</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="14">• Risk of seizure recurrence after a first seizure in adult.
• What factors are associated with recurrence?</td></tr>
<tr><td>Study Design</td><td colspan="14">Prospective</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Cases: All patients (inpatients, outpatients, private patients) > 16 years of age referred to one of the participants with first seizure. Included in study if neurologists believed to know the precipitant (cause) of seizures.
Patient tested after first seizure included.
Patients prescribed anticonvulsants after first seizure included in study.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">• Patients excluded if history revealed first seizure was not the first (absence in childhood).
• Seizure occurred as manifestation of an already diagnosed neurological disease such as glioma.
• Subjects who had more than one seizure in 24 hours.
• Subjects who had their second seizure after referral but before attending the neurological outpatient clinic.
• Anoxic seizures</td></tr>
<tr><td>Study population Characteristics</td><td colspan="13">• N=306 patients
• Age= Adults >16 years of age
• Types of seizures:
o Tonic-clonic = 97.5
o Partial = 2.2
o Other = 0.3
• See Figure G-12. Distribution of ages in 408 patients at the time of their first seizure.
• Refer to Table G-59</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Methods</td><td colspan="14">• Patients followed up after their initial seizure for 4 years.
• Neurologist obtained biographic details, descriptions of first seizures, family history of febrile convulsions or seizures, history of previous head injury.
• Neurologist arranged a pre-planned investigation on all patients to decide whether electroencephalography (EEG) and computerized tomography (CT) scanning were necessary. (See Table G-58).
• EEGs were coded according to a schemed usually by clinical neurophysiologist at referring center—completed by authors in some instances (A. H. or C. C.) which questioned whether or not EEG within normal limits by asking if epileptic or non-epileptic activity localized or generalized.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">• The Mantel-Cox used test used to evaluate the difference in probabilities of recurrence between groups of patients defined at the design stage of the study.
• Probability of < 0.05 was regarded as significant.
• 95% confidence interval for the probability of recurrence was calculated at approximately 3, 12, and 24 months after first seizure.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Quality Score = 6.7</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>N</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Risk of seizure recurrence tested.</td></tr>
<tr><td>Results</td><td colspan="14">• Age was not significantly a predictive factor (noted that younger subjects < 50 years are less likely to have a recurrent seizure.
• Higher probability for patients with a family history in first-degree relatives of either febrile convulsions (3.8% of subjects) or epilepsy (13.7%); no statistical significance.
• Seizure type judged by both EEG and clinical criteria did not reveal significant recurrence.
• Time of day at which initial seizure occurred associated with greater risk of recurrence. Risk of subsequent seizures was higher if the initial seizure occurred between the hours of midnight and breakfast time than any other time of day (p<0.003).
• 95% of 408 subjects had an EEG which shows that rate of relapse was not significantly higher for those subjects recruited within 8 weeks of their initial seizure if the EEG was abnormal.</td></tr>
</table>

	• *92% of 408 subjects had cranial CT scans soon after the first seizure and recruitment. If tumors were present on initial scan risk of subsequent seizures were higher than subjects with normal scans.* • No significant difference between rates of recurrence in subjects prescribed anticonvulsant drugs. • If all 408 patients included and studies combine family history of febrile convulsion and epilepsy under the multivariate analysis, then family history nearly reached the significance level (p=.057); variables analyzes also revealed that time of day was a significant predictive factor. • Figure G-13 suggests that recurrence rates are much higher for those patients recruited within the first eight weeks after a seizure than those recruited more than eight weeks after the first seizure; would appear more likely that patients waiting more than 8 weeks for neurological outpatient appointments and potential recruitment studies had already experienced further seizure by the time they were seen by neurologist. Thus became ineligible for the study. • *Probabilities used indicate 52% of all subjects seen within the first week of their first seizure will have a second seizure by the end of 3 years. See* Table G-60, Table G-61, Table G-62.
Authors' Comments	• *Sex, type of seizure, and features of electroencephalogram were not of predictive value.* • Computerized tomographic scanning revealed tumors in 3% of subjects—these individuals likely to have recurrent seizures. • Question arises by author whether or not anticonvulsants should be used more readily to control the high rate of recurrence. • It was decided that it would be inappropriate to withdraw patients prescribed anticonvulsants after first seizure. I could be argued that those patients who were treated were those thought by their doctors to be at particular risk of recurrence. Author felt that these subjects should be included as did Annegers et al in recent study.
Reviewer's Comments	• Study reveals that EEGs were sometimes coded by the authors instead, who may or may not possess the same level of expertise; which may therefore create discrepancies.

Table G-58. Investigations performed in 408 subjects after their first seizure

Investigation	%
Skull X-ray	91
Cranial CT scan	92
EEG	95
Chest X-ray	85
Routine blood count	91
Ca^{++}, glucose, liver function tests	91
Syphilis serology	88

Table G-59. Type of initial seizure (n=408)

Type	%	
Tonic-clonic		
No evidence of partial onset	85·3	97·5
Clinical evidence of partial onset	12·2	
Partial		
Complex	1·5	2·2
Simple	0·7	
Other		0·3

Table G-60. Chances of recurrence at intervals after first seizure (%)

—	By 3 mo	6 mo	1 yr	2 yr	3 yr
If there has been no recurrence within 1 wk	20 (n[1] = 100)	28 (74)	39 (49)	49 (21)	52
If there has been no recurrence within 4 wk	25 (n[2] = 101)	32 (72)	40 (52)	49 (30)	49
If there has been no recurrence within 8 wk	10 (n[3] = 105)	19 (93)	32 (63)	38 (34)	43
If there has been no recurrence after 8 wk have elapsed	(n[4] = 95)	9 (89)	11 (77)	15 (51)	22
From overall data of Annegers et al'	21	30	36	—	48

n[1] to n[4] refer to numbers of subjects on which recurrence in each row is based. Subsequent numbers in parentheses in the same row refer to numbers of subjects entering each period (ie, less recurrences and losses to follow-up).

Table G-61. Abnormalities seen on EEG after first seizure (late entry group excluded)

—	No	%
Normal	137	*46·4*
Localised epileptic activity	28	*9·5*
Generalised epileptic activity	51	*17·3*
Localised or generalised non-epileptic activity	79	*26·8*
Total	295	*100*

Table G-62. Effect of combination of clinical features upon rate of recurrence at 1 year after a first seizure in 304 adults (Late entry group excluded)

Age <50 Seizure between midnight and 8.59 am Family history of epilepsy/febrile convulsions	% recurred	Estimated probability of recurrence (95% confidence interval)
28 had none of these features, 5 recurred	18	0·18 (0·075–0·28)
177 had one of the features, 54 recurred	31	0·30 (0·25–0·36)
84 had two of the features, 35 recurred	42	0·43 (0·35–0·51)
15 had all three features, 9 recurred	60	0·56 (0·42–0·70)

Figure G-12. Distribution of ages in 408 patients at the time of their first seizure.

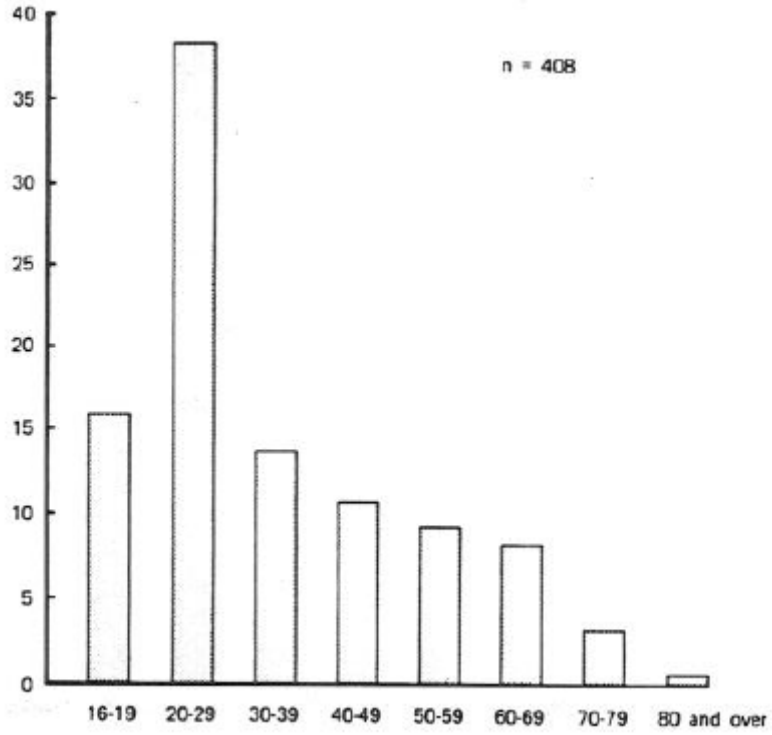
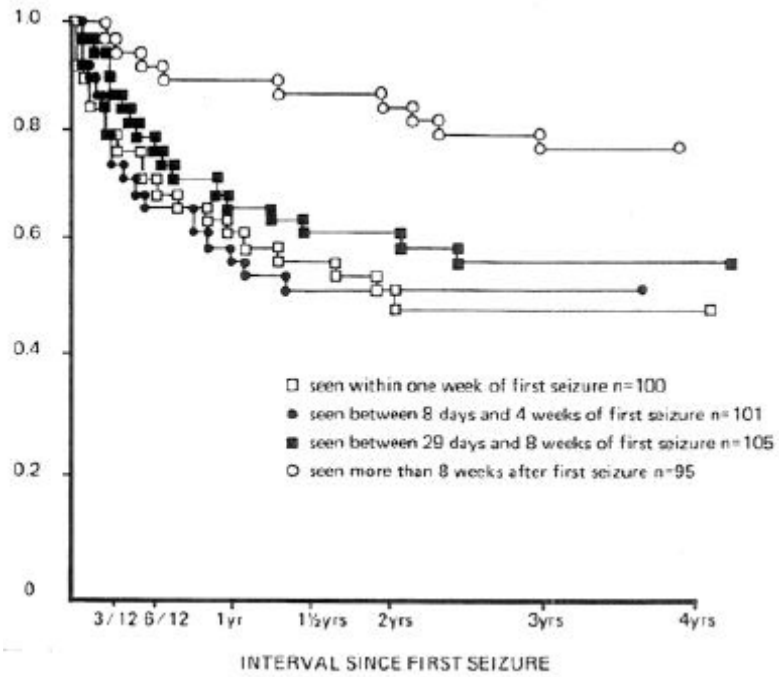
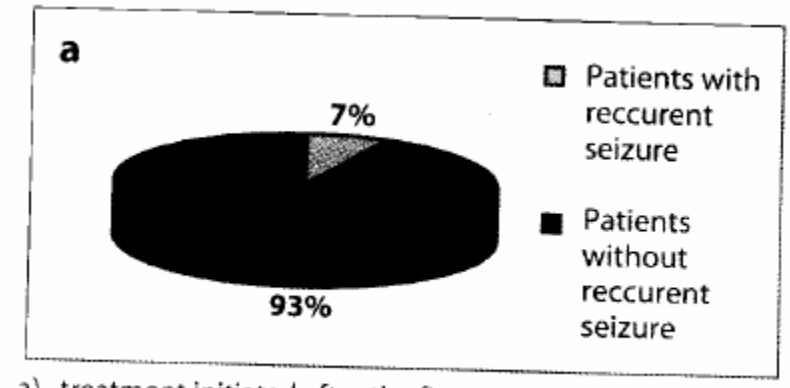


Figure G-13. Probability of remaining free from further epileptic seizures as a function of interval before recruitment into the study

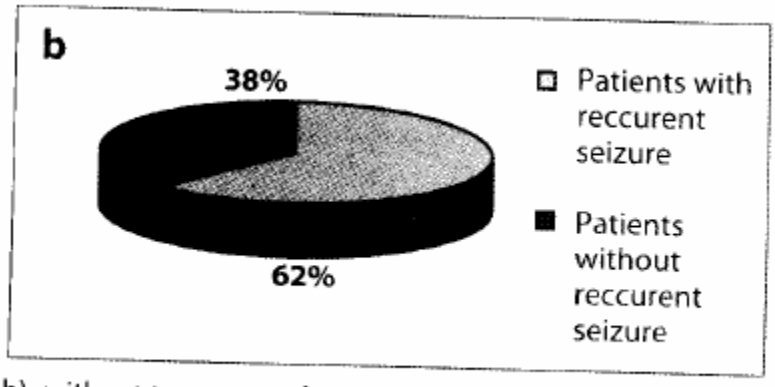


<table>
<tr><td colspan="15">Reference: Kollar B, Buranova D, Goldenberg Z, Klobucnikova K, Varsik P. Solitary epileptic seizure – the risk of recurrence. Neuro Endocrinol Lett 2006: 27 (1-2); 16-20.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td></tr>
<tr><td></td><td>√</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="6">• What is the risk of recurrence for patients who have experienced a solitary unprovoked seizure?
• What are probable risk factors pertaining to seizure recurrence?</td></tr>
<tr><td>Study Design</td><td colspan="6">Retrospective Case Study</td></tr>
<tr><td rowspan="3">Population</td><td>Inclusion Criteria</td><td colspan="5">• Patients dispensary of the 1st Department of Neurology, Medical Faculty of Comenius University and Faculty Hospital in Bratislava, Slovakia.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="5">NR</td></tr>
<tr><td>Study population Characteristics</td><td colspan="5">Population
N= 30
Sex
16 females
14 males
Age
Range= 19 to 81 years
See Table G-64. The patient group evaluated for seizure recurrence after the first unprovoked epileptic seizure (n=30).</td></tr>
<tr><td></td><td>Generalizability to CMV drivers</td><td colspan="5">Unclear</td></tr>
<tr><td>Methods</td><td colspan="6">• Information collected from clinical documentation and from completely filled out forms of patient history.
• Patients were followed up for a period of 3-7 years.
• Patient count with recurrent seizure established and time between first and second seizures documented.
• Evaluation completed for patient febrile seizures, family history of epilepsy, time of seizure occurrence, neurological status, type of convulsion, EEG findings, and influence of antiepileptic treatment initiation after the first seizure (drug chosen according to standard therapeutic guideline) used to forecast possible seizure recurrence.</td></tr>
<tr><td>Statistical Methods</td><td colspan="6">• Binomial division test used for qualitative characters according to Ondrejka and Mikulecky for statistical comparison of group differences.
• Statistical significance of p<0.001.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Quality Score = 5.6</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>NR</td><td>Y</td><td>NR</td><td>NR</td><td>N</td><td>Y</td><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="6">Risk and rate of seizure recurrence.</td></tr>
<tr><td>Results</td><td colspan="6">• Out of group of 30 patients that were registered, 11 cases of epileptic seizure recurrence over follow-up period (at least 3 years); 19 patients epileptic seizure did not recur.
• Risk of seizure recurrence in group of patients after first unprovoked epileptic seizure (UES) has been 30% up to 1 year and 33.33% up to 3 years.
• Patients with family history of epilepsy, structural and progression CNS lesion, partial convulsions and epileptiform EEG findings were at higher risk (but no statistically significant).
• Significance factor regarding recurrence of epileptic seizure appeared to be initiation of treatment after the first unprovoked paroxysm (p<0.001).
• See Figure G-14 for complete details.</td></tr>
<tr><td>Authors' Comments</td><td colspan="6">• Factors such as structural CNS lesion, symptoms and signs of focal cerebral lesion, presence of partial epileptic convulsions and epileptiform EEG findings have not only a certain inner connection, but can equally participate in seizure initiation as a so called "locus minoris resistentiae". Table G-64.
• 514 patients treated right after the first UES and registered seizure recurrence only in one patient (7.14%). In 16 patients without treatment initiation 10 patients (62.5%) registered seizure recurrences.
• Initiation of antiepileptic medication in patients after solitary unprovoked epileptic treatment was the only factor decreasing the risk of seizure recurrence in our patient group and at the same time had a statistical significance.
• In spite those statements initiation of antiepileptic treatment should not be automatic, but individual approach with considering of all risks and probability of seizure recurrence should be implemented.</td></tr>
</table>

Figure G-14. Seizure Recurrence in Patients after Solitary Unprovoked Epileptic Seizure.



a) treatment initiated after the first seizure



b) without treatment after the first seizure

Table G- 63. The patient group evaluated for seizure recurrence after the first unprovoked epileptic seizure (n=30).

Pat. No. initials	Age at occurrence of the 1st epileptic seizure, sex	Clinical type of the 1st epileptic seizure	Etiology	EEG, EEG after SD, LTM	Obj. neurological examination	History of febrile seizures	Family history of epilepsy positive?	AE initiation after the 1st epileptic seizure?	Occurrence of the 1st epileptic seizure day -night? sleep – alert?	Recurrence after the 1st epileptic seizure?	If yes, after what time period	Follow-up	
												Length	Recurrence after the 2nd seizure
1.JR	34 ys, F	2D	I	N	N	no	no	no	D-A	no	–	5 ys	–
2.MB	26 ys, F	2C	LS	GNA	N	no	yes	no	D-A	yes	After 5 ys	5 ys	–
3.TC	19 ys, M	2C	I	N	N	no	no	no	n-S	yes	After 1 y	4 ys	yes
4.OD	51 ys, F	1B	C	FNA	N	no	no	yes	D-A	no	–	4 ys	–
5.JV	46 ys, M	2C	LS	FEA	N	no	yes	no	D-A	yes	After 3 ys	6 ys	yes
6.IS	39 ys, M	2C	I	N	N	no	no	no	D-A	yes	After 7 mo	6 ys	no
7.MU	34 ys, F	2C	I	N	N	no	no	no	n-S	yes	Next day	3 ys	no
8.MK	22 ys, F	1C	C	FNA	N	no	no	yes	D-A	no	–	3 ys	–
9.MS	23 ys, F	1C	C	FNA	N	no	no	yes	D-A	no	–	3 ys	–
10.EB	50 ys, F	1C	C	FNA	N	no	no	no	D-A	yes	After 6 days	3 ys	yes
11.ĽV	52 ys, F	1C	LS	GNA	P	no	no	yes	D-A	no	–	3 ys	–
12.HK	38 ys, F	2D	LS	GEA	N	no	no	yes	D-A	no	–	7 ys	–
13.MK	40 ys, F	2C	LS	GNA	P	no	no	no	n-S	yes	After 3 mo	7 ys	no
14.MM	20 ys, F	2C	LS	GEA	P	no	no	yes	D-A	no	–	4 ys	–
15.JR	44 ys, M	1C	LS	GNA	P	no	no	yes	D-S	yes	After 1 y	6 ys	no
16.ĽN	50 ys, M	2D	LS	N	N	no	no	no	D-A	no	–	5 ys	–
17.AE	81 ys, F	1A	LS	GNA	P	no	no	no	D-A	no	–	4 ys	–
18.ĽK	46 ys, M	1C	LS	GNA	N	no	no	no	D-A	no	–	5 ys	–
19.MD	24 ys, M	1C	LS	N	N	no	no	yes	D-A	no	–	6 ys	–
20.BB	60 ys, F	1A	LS	FEA	P	no	no	no	D-A	yes	After 2 ws	3 ys	no
21.JH	78 ys, M	1C	LS	FNA	P	no	no	no	D-A	yes	After 2 ws	3 ys	yes
22.JR	64 ys, M	2C	LS	GNA	P	no	no	no	D-A	no	–	6 ys	–
23.MG	53 ys, F	2C	LS	N	N	no	no	yes	n-S	no	–	6 ys	–
24.AV	57 ys, F	2D	LS	FEA	P	no	no	no	n-S	no	–	4 ys	–
25.PK	9 ys, M	2C	LS	FEA	N	no	no	yes	D-A	no	–	5 ys	–
26.JŠ	22 ys, M	1C	LS	FNA	N	no	no	yes	D-A	no	–	4 ys	–
27.MU	21 ys, F	2C	LS	GNA	N	no	no	yes	D-A	no	–	5 ys	–
28.MP	21 ys, M	1C	LS	FEA	N	no	no	yes	D-A	no	–	5 ys	–
29.AD	19 ys, M	1C	LS	GNA	N	no	no	no	D-A	yes	After 1 mo	5 ys	yes
30.BK	35 ys, M	1C	LS	FNA	N	no	no	yes	n-S	no	–	6 ys	–

Notes: A – alert, AE – antiepileptic, C – cryptogenic, D – day, EEG – electroencephalography, EEG after SD-electroencephalography after sleep deprivation, F – female, FEA – focal epileptiform EEG activity, FNA – focal non-epileptiform EEG activity, GEA – generalized epileptiform EEG activity, GNA – generalized non-epileptiform EEG activity, I – idiopathic, LS – late symptomatic, LTM – long-term EEG monitoring, M – male, mo – months, N – normal, n – night, No – number, P – pathological, Pat. – patient, S – sleep, y – year, ys – years, ws – weeks, 1A – simplex partial seizures, 1B – complex partial seizures, 1C – partial seizures with secondary generalization, 2C – generalized tonic-clonic seizures, 2D – generalized tonic seizures

Table G-64. Individual Factors in Relation to Seizure Recurrence after the 1st Unprovoked Epileptic Seizure

		Patients with recurrence after the 1st epileptic seizure (n=11)	Patients without recurrence after the 1st epileptic seizure (n=19)	Recurrence/ recurrence + non-recurrence ratio	Significant factor in terms of recurrence?
Etiology	idiopathic + cryptogenic	4	5	4/9 (44.44%)	No
	Late symptomatic	7	14	7/21 (33.33%)	
Occurrence of epileptic seizure	day – alert	7	15	7/22 (31.81%)	No
	sleep – awakening	4	4	4/8 (50%)	
Type of seizure	generalized	6	9	6/15 (40%)	No
	partial	5	10	5/15 (33.33%)	
EEG finding	normal + non-epileptic abnormity	9	14	9/23 (39.13%)	No
	epileptic abnormity	2	5	2/7 (28.57%)	
Objective neurological examination	Normal	7	14	7/21 (33.33%)	No
	pathological	4	5	4/9 (44.44%)	
Febrile seizure occurrence?	Yes	0	0		
	No	11	19	11/30 (36.67%)	
Positive family history for epilepsy?	Yes	2	0	2/2 (100%)	No
	No	9	19	9/28 (32.14%)	
AE treatment initiation after the 1st epileptic seizure?	Yes	1	13	1/14 (7.14%)	**Yes**
	No	10	6	10/16 (62.5%)	
Recurrence after the 1st epileptic seizure till...	3 months	6			
	6 months	9			
	1 y	9			
	3 y	10			
	5 y	11			

Notes: AE- antiepileptic, EEG- electroencephalography, n- number of patients

<table>
<tr><td colspan="15">Reference: van Donselaar CA, Geerts AT, Schimsheimer RJ. Idiopathic first seizure in adult life: who should be treated? BMJ vol 302: 1991: 620-623.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td></tr>
<tr><td></td><td></td><td></td><td>√</td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="6">To assess the accuracy of the diagnosis, recurrence rate, and fate after the first recurrence in adult patients with an untreated idiopathic first seizure.</td></tr>
<tr><td>Study Design</td><td colspan="6">Prospective Case series (single blinded)</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="5">• All patients with a presumed idiopathic first seizure who were referred to one university hospital and three general hospitals in the Netherlands during March 1986 to March 1988.
• Patients were admitted if it appeared to be no clinical cause for seizure; patients with seizures that may have been caused by sleep deprivation or stress.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="5">• Patients who had seizures other than febrile convulsion in the past.
• Patients presenting with status epilepticus.
• Patients that may have experienced a seizure lasting longer than 30 minutes.
• Patients who had experienced extreme conditions such as not sleeping for several days.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="5">Population
N = 165
Sex
Male = 97
Female= 68
Age
Range= 15 to 85 years
Mean age= 38
Patients had all been unconscious with:
Myoclonic jerks= 52
Stiffening= 8
Tongue biting= 7
Combination of symptoms= 95
Complex partial seizures= 2
See Table G-65. Potential Predictive Factors for Risk of Recurrence of Seizures</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="5">Unclear</td></tr>
<tr><td>Methods</td><td colspan="6">• Diagnosis was based on the description of the episodes according to specified criteria.
• All patients discussed by 3 neurologists before admission
• All four health facilities referred a total of 226 patients (61 excluded for attendance and multiple pre-diagnosed conditions).
• To analyze recurrence rates, 9 patients who had major abnormalities on computed tomography, 3 patients experiencing a second seizure within 24 hours after the first and 2 patients who were treated immediately with antiepileptic drugs were all excluded.
• Standard electroencephalography was done on 151 patients.
• All electroencephalograms were read by one neurologist who had no access to the clinical information (blinded); rated as normal, showing epileptic discharges or showing other abnormalities.
• Length of follow up was determined by time of admission and ranged from 1 to 2 years.
• 25 of 58 patients with an idiopathic first seizure who had a recurrence were started on drugs immediately after first recurrence; treatment postponed until more occurrences in 26 patients and 6 patients were not given any drugs yet had not further recurrences.</td></tr>
<tr><td>Statistical Methods</td><td colspan="6">• Follow up were analyzed using Kaplan-Meier survival curve.
• 95% confidence interval used for rate recurrence.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Quality Score = 6.1</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>N</td><td>NR</td><td>Y</td><td>Y</td><td>NR</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="6">Rate of recurrence, accuracy of diagnosis examined.</td></tr>
</table>

Results	Overall recurrence rate for 151 patients with idiopathic untreated isolated seizure in 151 patients confirmed by computed tomography was 40% (95% confidence interval 32% to 48%) at 2 years. Predictive factors for second seizure: • Higher recurrence rate associated with younger age, occurrence of first seizure during sleep on awakening, and tongue biting. See Table G-65. • *Family history, provocative circumstances, and sex did not correlate significantly with the risk of recurrence.* • *Association of recurrence rates with interval between first seizure and first visit to hospital were inconsistent.* • Computed tomography showed the initial clinical diagnosis to be wrong in 5.5% of the patients; follow-up led to the initial clinical diagnosis being doubted in an additional 6%. • Standard electroencephalogram showed epileptic discharges in 16 patients; 15 who experience second seizure within 2 years (1 remained seizure-free during 16 month follow-up; cumulative risk of recurrence at 2 years was 100%). • Cumulative recurrence rate was 40% in 68 patients with non-epileptic abnormalities and 25% in 67 patients with normal findings. See Table G-66. Cumulative recurrence rates based on findings in combined standard and sleep deprivation electroencephalograms in 151 patients with idiopathic first seizures.. • Standard and combined electroencephalograms identified 26% and 47% of those who had recurrences respectively. • The specificity of electroencephalography was 99% for standard conditions and 91% for the combined electroencephalograms. • Of the 58 patients with an idiopathic first seizure who had recurrence, 40 (70%) patients became free of seizure, 8 (14%) had sporadic seizures, 9 (16%) continued to have seizure despite taking drugs one year follow up.
Authors' Comments	• Author's recurrence rate of 40% at 2 years agrees with the results of Hopkins et al, who found a recurrence rate of 45%. • First year of treatment crucial for the long term prognosis. Found that 17 (30%) of patients who had second seizure (11% of the original 151 patients) did not become completely seizure free within one year. • If all patients treated immediately after their first seizure intractability might be prevented in some patients. • Risk of recurrence if both electroencephalograms appeared normal was low. • Most other studies show an increased risk of recurrence in patients with electroencephalographic abnormalities, however, authors' reliability of visual interpretation of electroencephalograms is moderate. • The decision to initiate or delay treatment should be based on electroencephalographic findings.
Reviewer's Comments	2 patients lost to follow up were included in analysis

Table G-65. Potential Predictive Factors for Risk of Recurrence of Seizures

Predictive factor	No of patients (n=151)	Recurrence rate at 2 years (%) (95% confidence interval)	Observed difference (%) (95% confidence interval)
Age:			
15-24	50	50 (36 to 64)	11 (−9 to 31)*
25-44	52	39 (25 to 43)	10 (−9 to 29)†
45-85	49	29 (16 to 42)	21 (2 to 40)
Family history§:			
Negative	133	40 (31 to 49)	
Positive	16	44 (20 to 68)	4 (−22 to 30)‡
Interval between first seizure and first visit:			
<24 Hours	77	31 (20 to 42)	22 (4 to 40)*
1-14 Days	54	53 (39 to 67)	18 (−7 to 43)†
>14 days	20	35 (14 to 56)	4 (−20 to 28)‡
Time of occurrence:			
During day	118	32 (23 to 41)	40 (20 to 60)
While asleep or awakening	33	72 (54 to 90)	
Provocative circumstances:			
Absent	100	44 (34 to 54)	12 (−5 to 29)
Present	51	32 (19 to 45)	
Standard electroencephalogram:			
Epileptic discharges	16	100 (70 to 100)	60 (40 to 80)*
Other abnormalities	68	40 (29 to 52)	15 (−1 to 31)†
Normal	67	25 (14 to 36)	75 (55 to 95)‡
Combined results of standard sleep deprivation electroencephalograms:			
Epileptic discharges	35	81 (66 to 97)	42 (22 to 62)*
Other abnormalities	65	39 (27 to 51)	27 (12 to 42)†
Normal	51	12 (3 to 21)	69 (51 to 87)‡
Tongue bite‡:			
Absent	81	27 (17 to 37)	28 (12 to 44)
Present	70	55 (43 to 67)	
Sex:			
Male	91	35 (25 to 45)	12 (−5 to 29)
Female	60	47 (34 to 60)	

Table G-66. Cumulative recurrence rates based on findings in combined standard and sleep deprivation electroencephalograms in 151 patients with idiopathic first seizures.

	Epileptic discharge			Other abnormalities			Normal			All patients		
Month	Recurrence rate (%) (95% confidence interval)	No at risk	No who had had recurrences (No censored*)	Recurrence rate (%) (95% confidence interval)	No at risk	No who had had recurrence (No censored*)	Recurrence rate (%) (95% confidence interval)	No at risk	No who had had recurrence (No censored*)	Recurrence rate (%) (95% confidence interval)	No at risk	No who had had recurrence (No censored*)
0		35			65			51			151	
6	57 (41 to 74)	15	20	26 (16 to 37)	48	17	8 (1 to 15)	46	4 (1)	27 (20 to 34)	109	41 (1)
12	66 (50 to 81)	12	3 .	34 (22 to 45)	43	5	10 (2 to 18)	45	1	33 (26 to 41)	100	9
18	75 (61 to 90)	7	5 (2)	37 (25 to 49)	35	2 (6)	12 (3 to 21)	31	1 (13)	38 (30 to 46)	73	6 (21)
24	81 (66 to 97)	2	1 (4)	39 (27 to 51)	23	1 (11)	12 (3 to 21)	13	(18)	40 (32 to 48)	38	2 (33)

*Not all patients were scheduled for follow up of two years.

Study Summary Tables for Key Question 5

Reference: Dilorio C, Faherty B, Manteuffel B. Cognitive-Perceptual Facotrs Associated with Antiepileptic Medication Compliance. Research in Nursing & Health: 1991: 14,329-328.

Key Questions Addressed	1	2	3	4	5	6
					√	

Research Question: To determine if selected cognitive-perceptual variables discriminated between individuals who complied with antiepileptic medication therapy and those who did not.

Study Design: Case Series

Population

Inclusion Criteria: Subjects selected from an outpatient epilepsy clinic serving low socioeconomic status patients who:

- spoke English as their first language
- had a history of seizures
- were 18 years of age or older
- were currently taking antiepileptic drugs
- had a willingness to participate

Exclusion Criteria: NR

Study population Characteristics

	Compliant (n=39)	Noncompliant (n=25)
Age		
Mean	35.56	36.56
SD	11.26	13.68
Gender		
Male	21 (54%)	12 (48%)
Female	18 (46%)	13 (52%)
Race		
Black	26 (67%)	19 (76%)
White	13 (33%)	6 (24%)

See Table G-67

Compliers and noncompliers did not differ significantly on any of the demographic or seizure/medication related variables.

Generalizability to CMV drivers: Unclear

Methods

- Persons interested in participating were introduced to the researcher who explained the study in more depth; subjects signed informed consents and completed a demographic data sheet.
- 77 patients initially asked to participate, 73 agreed. Of 73, 9 excluded for reasons such as incomplete questionnaires, outlying scores greater than 3 standard deviations, or compliance undetermined.
- Measurement of compliance included both objective and subjective components:
  - Objective:
    - Compliance defined by an average of serum level of antiepileptic medication in the range designated as therapeutic by the laboratory at the study site.
    - Noncompliance defined by an average serum level of antiepileptic medication 30% or more below therapeutic range
    - Antiepileptic blood levels obtained the day of the subject's participation and all antiepileptic drug levels obtained during the preceding 3 months were averaged.
    - Mean value was used to classify the subject as compliant or noncompliant
  - Subjective:
    - Physicians and nurses identified potential subjects from patients arriving for their regularly scheduled appointments.
    - Classified as compliant or noncompliant based on historical knowledge of the patient and his or her therapy.
- Data collected for 6 months; one researcher attended the weekly epilepsy clinic held at the clinic.
- Subjective measure for compliance involved requesting nurses and physicians to classify patients as noncompliant or compliant based on historical knowledge of the patient and his or her therapy.

	• Discriminant analysis was conducted to find which variables differentiate the compliant from the noncompliant subjects													
Statistical Methods	T tests and chi-square analyses used to compare patient groups.													
Quality assessment	Study quality=5.58	1	2	3	4	5	6	7	8	9	10	11	12	13
		Y	Y	Y	N	Y	N	Y	Y	NR	Y			
	Moderate	14	15	16	17	18	19	20	21	22	23	24	25	
Relevant Outcomes Assessed	Level of compliance measured against treatment effectiveness.													
Results	• Patient's whose serum levels fell below therapeutic level, but not more than 30% below, were excluded from the analysis to prevent classifying some subjects incorrectly as noncompliant for greater accuracy. • Only subjects with 100% congruence between the objective and subjective measures were included in the analysis. • *Intimacy/assistance showed a significant difference between compliant (M=51.36) and noncompliant (M=56.48) subjects, t(62)=1.99, p=.05.* o Compliers who expressed higher levels of unpredictability about the course and outcome of epilepsy might perceive unpredictability as a threat and do what is expected to keep the condition under control o Noncompliers might be more likely to engage in risky behaviors regarding their medication regimen because they do not perceive unpredictability as a threat.													
Authors' Comments	• The findings revealed that intimacy/assistance, social integration/affirmation or worth, unpredictability, and ambiguity was helpful in discriminating compliant from noncompliant individuals. • The relationships between uncertainty, social support, and compliant behaviors need to be examined in more diverse populations. • It is important to replicate this study with another group of people with epilepsy.													

Table G-67. Comparison of Demographic Information for Compliant and Noncompliant Subjects

Variable	Compliant	Noncompliant
Age		
Mean	35.56	36.56
SD	11.26	13.68
Gender		
Male	21 (54%)	12 (48%)
Female	18 (46%)	13 (52%)
Race		
Black	26 (67%)	19 (76%)
White	13 (33%)	6 (24%)
Education in years		
Mean	11.00	10.80
SD	2.08	2.50
Marital status		
Never married	20 (51%)	12 (48%)
Married	6 (15%)	4 (16%)
Divorced	5 (13%)	7 (28%)
Separated	5 (13%)	0
Widowed	3 (8%)	2 (8%)
Employment		
Unemployed	30 (77%)	17 (68%)
Employed	9 (23%)	7 (28%)
Retired	0	1 (4%)

Table G-68 Comparison of Seizure-Related and Medication-related Information for Compliant and Noncompliant Subjects

Variable	Compliant	Noncompliant
Number of years with seizures		
Mean	18.69	13.40
SD	11.97	10.83
Seizure type		
Simple partial	1 (2%)	0
Complex partial	14 (36%)	11 (44%)
Partial with generalized	17 (44%)	6 (24%)
Generalized	7 (18%)	8 (32%)
Number seizure last year		
Mean	23.44	13.36
SD	36.64	19.99
Number of weeks since last seizure		
Mean	14.59	10.80
SD	24.28	23.07
Number of seizure druge		
Mean	1.49	1.44
SD	.56	.51
Total doses		
Mean	3.46	2.68
SD	1.83	1.65

<table>
<tr><td colspan="15">Reference: Kemp S, Feely M, Hay A, Wild H, Cooper C. Psychological factors and use of antiepileptic drugs: Pilot work using an objective measure of adherence. Psychology, Health & Medicine 2007:107-113.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td></tr>
<tr><td></td><td></td><td></td><td></td><td>√</td><td></td></tr>
<tr><td>Research Question</td><td colspan="6">To determine the influence of individuals' beliefs about epilepsy, beliefs about medication and a range of neuro-epilepsy variables on drug adherence among a sample of individuals with epilepsy.</td></tr>
<tr><td>Study Design</td><td colspan="6"></td></tr>
<tr><td rowspan="3">Population</td><td>Inclusion Criteria</td><td colspan="5">Individuals diagnosed with epilepsy recruited for a local epilepsy outpatient clinic.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="5">NR</td></tr>
<tr><td>Study population Characteristics</td><td colspan="5">Population
n=37
Sex
Females (18)
Males (19)
Age (years)
Range: 17-79
Mean: 40.77
See Table G-69
No difference between high and low compliers in terms of age, age at epilepsy onset and duration of epilepsy.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="5">Unclear</td></tr>
<tr><td>Methods</td><td colspan="6">• Date collected via clinical interview and questionnaire methods.
• Participants were taking either Lamotrigine or Lamotrigine and a low-dose Phenobarbital marker.
• Adherence with drug treatment was determined by an objective measure using low-dose Phenobarbital as an indicator of adherence and, or measurement of antiepileptic drug levels.
• Low levels of Phenobarbital taken by the group taking Lamotrigine and a low-dose Phenobarbital marker produced were measured by high performance liquid chromatography procedure.
• Data from the Lamotrigine and a low-dose Phenobarbital group was used to categorize adherence of the Lamotrigine group.
• 5 point rating scale cross derived and checked by two of the authors:
o 5= excellent adherence
o 4= good adherence
o 2-3= incomplete/partial adherence
o 1= poor adherence</td></tr>
<tr><td>Statistical Methods</td><td colspan="6">• Given non-normal distribution of the adherence scores, non-parametric tests were used. P<0.01 used to account for large correlations.
• Mann-Whitney tests used.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Study quality=6.15</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="6">Relationship between clinical variables and adherence.</td></tr>
<tr><td>Results</td><td colspan="6">• No difference between males and females in terms of age, age at epilepsy onset, duration of epilepsy and time since last seizure.
• Samples was splint into high and low compliers by the median adherence scores of 3.9
• Adherence scores were skewed with a mean (SD) of 3.69 (1.20). See Table G-70.
• Patients with low adherence scores had significantly less time since last seizure relative to high compliers.</td></tr>
<tr><td>Authors' Comments</td><td colspan="6">• Participation rate was 74%.
• Overall, data did not support an association either between cognitive representations of epilepsy and drug adherence or between beliefs about drug therapy and adherence.
• The study used an abbreviated version of the Kemp and Morley (2001) measure.</td></tr>
</table>

	• Future work should consider using the full Kemp and Morley (2001) measure or an alternative. • A detailed understanding of drug adherence remains elusive. • Limitations of study include: o Sample size constrained by the effort involved in attaining the objective adherence measurement o Data suffered from low power and risk of Type 2 error o Low alpha reliabilities on certain scales of the illness representations measure

Table G-69. Demographic and Clinical Characteristics

Mean age (years)	40.77, range (17–79)
Male: female	19:18
Mean age at epilepsy onset (years)	25.86, range (0–77)
Mean duration of epilepsy (years)	14.51, range (1–63)
Mean time since last seizure (days)	200.78, range (1–1642)
Adherence score (range 1–5):*	<3.9 (n=15) low adherence >3.9 (n=22) high adherence
Mean adherence score	3.69 (SD=1.20)

*Adherence scores were obtained on 37 subjects.

Table G-70. Correlations between Illness Representations, Psychological Status and Adherence

Scale	Subscale	Number of items	Alpha
BMQ	Specific—Necessity	5	.76
	Specific—Concerns	5	.62
	General—Overuse	4	.76
	General—Harm	4	.53

Reference: Kraus GL, Krumholz A, Carter RC, Li G, Kaplan P. Risk factors for seizure-related motor vehicle crashes in patients with epilepsy. Neurology 52. 1999: 1324-1329.

Key Questions Addressed	1	2	3	4	5	6
					√	

Research Question: To determine the influence of clinical risk factors associated with seizure-related motor vehicle crashes.

Study Design: Retrospective Case-Control

Population

Inclusion Criteria
- All patients in a chart review and from phone interviews using a questionnaire identified from 3 of Maryland hospital-based outpatient epilepsy clinics.
- Control patients were selected from an alphabetical review of patient files.
- Patients from general mid-Atlantic area and resided and drove across approximately equal ranges of urban, suburban, and rural settings.

Exclusion Criteria: Patients whose epilepsy was in remission off antiepileptic drug (AED) treatment during the study year or who had had epilepsy surgery during the study year.

Study population Characteristics

	Cases	**Controls**
Population	n=50	n=50
Age	38.5 (21-70)	39.8 (18-73)
Male/Female	41/9	41/9

See Table G-71

Generalizability to CMV drivers: Unclear

Methods
- Case and control patients were matched by having epilepsy (2 or more seizures), sex, and age (± 3 years) and were from the same clinic.
- Information on motor vehicle crashes came from reports by the patients.
- Study period for data collection was 12 months preceding crashes for cases and 12-month period beginning in mid-1996 for controls.
- 61 patients initially considered for study; 11 were excluded for clinical patterns such as AED compliance, seizure-free intervals, and number of seizure related accidents.
- **Questionnaire and data form collected containing the following information:**
  - Patient data (age, sex, presence of neurologic conditions other than epilepsy).
  - Crash variables (Seizure type, age at onset, etiology, frequency, number of crashes due to seizure, time of day of accident, provoking factors, presence of aura, number of cars, passengers and injuries, etc.).
  - Treatment factors (AEDs, dosages, changes, compliance).
  - Driving history (purpose of driving, hours per week, year(s) experience, total number of previous non-seizure related crashes).
  - Regulatory factors (whether patients were driving within time restriction required by their state, whether patients registered wit their motor vehicle agency before or following crashes, whether they continued driving after crashes).
- Odds ratio (OR) for accident risks were determined for approximately 3-month, 6-month, and 12-month seizure-free intervals.

Statistical Methods
- Possible risk factors were evaluated using conditional multivariate logistic regression.
- 95% confidence interval constructed for possible risk factors on the odds ratio (OR) for the probability of an accident during seizures for cases vs. controls.
- Wilcoxon singed-rank test.

Quality assessment

	1	2	3	4	5	6	7	8	9	10	11	12	13
Study quality=7.8	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	NR	Y
Moderate	14	15	16	17	18	19	20	21	22	23	24	25	

Relevant Outcomes Assessed: Factors associated with motor vehicle crash and relevancy to AED compliance

Results
- One of the risk factors associated with reduced odds for crashing were AEDs being reduced, stopped, or switched by patient's physician. (See Figure G-15)
- Patients who crashed had significantly higher seizure frequencies than control patients.
- Similar numbers of case and control patients reported missing AED doses or had low AED levels documenting poor medication compliance during the study period (approximately 1/3 of patients in both groups were classified as noncompliant).
- The 11 patients excluded from the case control study had crashes during their first epileptic seizure. None of these patients had neurologic

	conditions that had been identified before their accidents. • 10 patients (20%) crashed immediately after missing AED doses. • Other factors that reduce driving risks: long seizure-free intervals, reliable auras, having few prior non-seizure-related accidents and optimizing AED therapy.
Authors' Comments	• *Reducing or switching patients' AEDs significantly reduced, rather than increased, the odds of crashing. This appeared to be due to patients' having fewer seizures when their AEDs were consolidated.* • Possible owing to interactions with physicians, some patients were more regular in taking AEDs or became cautious in their driving. • Several patients did crash during the period when they were switching or tapering AEDs, suggesting that patients should not drive. • See Table G-72.

Table G-71. Patient Characteristics

Characteristic	Cases, n = 50	Controls, n = 50	Difference probability
Age, y (range)	38.5 (21–70)	39.8 (18–73)	*
M/F	41/9	41/9	*
Seizure types,† n (%)			
Simple partial	6 (12)	10 (20)	NS
Complex partial	26 (52)	26 (52)	NS
Secondarily generalized	13 (26)	12 (24)	NS
Generalized T-C	18 (36)	18 (36)	NS
Seizure frequency, average per month (range)	2.6 (0–60)	0.6 (0–6)	$p = 0.09$
Driving, h/week ± SEM	16.9 ± 2.4	13.3 ± 1.9	NS
Years driving ± SEM	18.9 ± 1.9	20.5 ± 1.8	NS
Purpose for driving, n (%)			
Commute/job	40 (80)	36 (72)	—
Other (family, shop, recreation)	19 (38)	26 (52)	—
Purpose for driving at time of crash, n (%)			
Commute/job	30 (60)		
Other	20 (40)		
Road types, n (%)	At crash	"Usual driving"†	NS
Freeway	12 (24)	20 (40)	
Other	38 (76)	30 (60)	

* Match criteria.
† Note: more than one value possible.

NS = not significant; T-C = tonic-clonic.

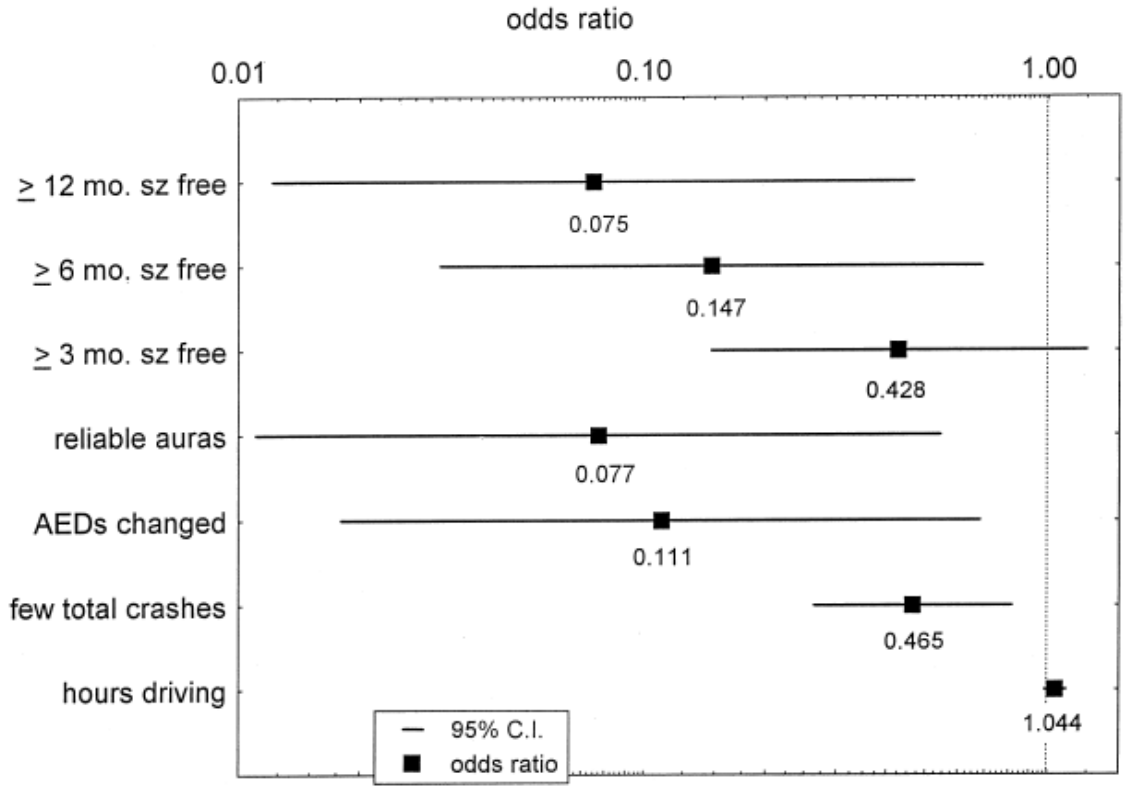
Table G-72. Factors associated with reduced odds of seizure-related crashes and possible recommendations for patients with epilepsy who drive

Factors associated with reduced odds of crashes	Possible recommendations for epilepsy patients who drive
Long seizure-free intervals	Comply with state mandated rules and seizure-free restriction, maximize seizure therapy, and consider long (6–12 mo) intervals to minimize risk further
"Reliable" auras*	Stop driving during auras; caution patients that reliable auras do not guarantee they will not crash while driving
Adjusting AEDs to reduce seizures	Optimize AED therapy to control seizures, advise limiting driving during AED adjustments
Few prior nonseizure-related motor vehicle crashes	Note importance of driving safety in general
Additional risk factors	
Not evident in the case control analysis, but directly linked to crashes	
First seizure while driving	Consider restricting driving for a period if at high risk for seizures (e.g., malignant brain tumor)
History of previous seizure-related traffic crashes	Caution patients about their increased risk for additional crashes, consider long (≥12 mo) seizure-free periods before driving
Missed AED doses	Reinforce the importance of AED compliance and advise patients not to drive after missing AED doses

* Auras "always" precede seizures.

AED = antiepileptic drug.

Figure G-15. Factors associated with decreased odds of motor vehicle crashes in patients with epilepsy



Reference: Peterson M, McLean S, Millingen K. A Randomized Trial of Strategies to Improve Patient Compliance with Anticonvulsant Therapy. Epilepsia Vol 25. No. 4: 1984: 412-417.

Key Questions Addressed	1	2	3	4	5	6
					√	

Research Question: What is the relationship between compliance with an anticonvulsant medication and treatment effectiveness?

Study Design: Randomized Control Trial (single blinded)

Population

Inclusion Criteria: Epileptic outpatients from the Royal Hobart Hospital who were consecutive attendees at outpatient clinics during a 4-month period; possessed hospital pharmacy prescription book and responsible for the administration of their own medication.

Exclusion Criteria: NR

Study population Characteristics:

Population:

N= 53 adult and teenage epileptic patients

Control group:	Intervention group:
Age Range:	Age Range:
19-74 years	18-64 years
(median age 35 years)	(median age 28 years)
Sex:	Sex:
11 females (42%)	12 females (44%)
15 males (58%)	15 males (56%)

See Table G-73

Generalizability to CMV drivers: Unclear

Methods

Patients evaluated prior to intervention and 6 months afterwards.

Assessment and patient compliance:

- Patients had plasma anticonvulsant levels measured by EMIT (Syva, Palo Alto, CA), provided that patients' medication regiment had not been altered during the preceding 2 weeks.
- Blood samples were taken between 3 p.m. and 4 p.m.
- Prescription record books of each patient were examined.
- Patients who had attended all scheduled clinic appointments during the previous 6 months were considered compliant.

Patients in the intervention group were subjected to a combination of compliance improving strategies:

- **Patient counseling:**

Patients counseled on goals of anticonvulsant therapy and importance of good compliance in keeping goals

- **Special Medication container:**

Patients provided with a Dosett Medication container and counseled on advantages and correct use of system

- **Medication/Seizure diary:**

Used for self recording of medication intake and seizures

- **Prescription refill and appointment keeping reminders:**

Used to collect prescription refills and attend clinical appointment.

Physicians treating patients did not know to which group they belong.

Statistical Methods

- Changes in compliance and control within the groups were statistically evaluated by McNemar tests for related samples, Wilcoxon matched-pair tests, Stuart-Maxwell tests, and student's paired t tests.
- Differences between two groups were assessed with chi square tests, Mann-Whitney tests, and Student unpaired t tests.

Study quality= 6.7	1	2	3	4	5	6	7	8	9	10	11	12	13	
	Y	Y	Y	Y	N	N	Y	Y	Y	Y	NR	Y	N	
Moderate	14	15	16	17	18	19	20	21	22	23	24	25		
	N	N	Y	NR	N	Y	Y	Y	Y	Y	NR	Y		

Relevant Outcomes Assessed: Compliance as measured by plasma anticonvulsant levels and medication refill frequencies, seizure recurrence, and treatment effectiveness.

Results	• Significant difference at follow-up (n=72 chi-square = 13.28, df = 2, p<0.005) due to a shift in subtherapeutic to therapeutic plasma levels in many intervention group patients (n= 41, Stuart-Maxwell chi-square = 13.78, df = 2, p<0.005). • There was no significant change with time in the distribution of plasma levels within the control group (n=31, Stuart-Maxwell chi-square = 1.0 df=2, p>0.10). • The reduction in the number of seizures for the intervention group – a decrease in median from 6 to 2.5 – was statistically significant (Wilcoxon T=38, n=21, p<0.001). • The change in seizure frequency for the control group was not significant (Wilcoxon T = 87.5, n = 21, p > 0.1). • Compare Table G-74 and Table G-75
Authors' Comments	• Results indicate that a combination of compliance-improving strategies significantly (easily incorporated into the routine management of individuals with epilepsy) improved compliance with anticonvulsant therapy, As a consequence, seizure frequency was, on average halved. • Author recommends similar strategic programs of compliance improving to ultimately reduce "disability and social handicap".

Table G-73. Patient Characteristics

Characteristics	Control group		Intervention group	
	Number of patients	Percentage	Number of patients	Percentage
Sex				
Female	11	42	12	44
Male	15	58	15	56
Age (years)				
<20	2	8	3	11
20–39	14	54	17	63
40–60	6	23	5	19
>60	4	15	2	7
Median	35		28	
Range	19–74		18–64	
Employment status				
Student	1	4	1	4
Not in employment	16	62	19	70
Full- or part-time employment	9	35	7	26
Type of epilepsy				
Primary generalized tonic-clonic	17	65	14	52
Partial with secondary generalization	3	12	5	19
Complex partial	4	15	4	15
Other	2	8	4	15
Anticonvulsant drugs				
Phenytoin	23	89	20	74
Carbamazepine	5	19	14	52
Sodium valproate	5	19	8	30
Other	5	19	3	11
Number of seizures in previous 6 months				
Median	4		6	
Range	0–51		0–55	

Table G-74. Anticonvulsant dosages and plasma levels prior to intervention.

Group	Phenytoin[a]			Carbamazepine			Sodium valproate		
	n	Dose[b] (mg/kg)	Plasma level/dose[c] (μmol/L/mg/kg)	n	Dose[b] (mg/kg)	Plasma level/dose[c] (μmol/L/mg/kg)	n	Dose[b] (mg/kg)	Plasma level/dose[c] (μmol/L/mg/kg)
Control	21	5.0 ± 1.6	8.2 ± 5.4	5	13.1 ± 1.8	2.0 ± 0.2	5	24.3 ± 4.2	20.0 ± 6.0
Intervention	19	5.5 ± 1.4	8.4 ± 4.3	14	12.4 ± 4.7	2.2 ± 1.1	8	23.6 ± 4.9	9.7 ± 2.8
Significance[d]		p > 0.2	p > 0.5		p > 0.5	p > 0.5		p > 0.5	p < 0.01

[a] Data on three patients receiving phenytoin who were lost at follow-up have been omitted.
[b] Mean daily prescribed dose (±SD).
[c] $\frac{\text{Mean steady-state plasma level}}{\text{Mean daily prescribed dose}}$ (±SD).
[d] By Student's unpaired *t* test.

Table G-75. `Anticonvulsant dosages and plasma level after intervention

	Phenytoin[a]			Carbamazepine			Sodium valproate		
Group	n	Dose[b] (mg/kg)	Plasma level/dose[c] (μmol/L/mg/kg)	n	Dose[b] (mg/kg)	Plasma level/dose[c] (μmol/L/mg/kg)	n	Dose[b] (mg/kg)	Plasma level/dose[c] (μmol/L/mg/kg)
Control	21	5.7 ± 1.4	7.1 ± 4.6	5	12.2 ± 5.0	1.9 ± 1.5	5	25.4 ± 7.1	20.2 ± 7.9
Intervention	19	5.0 ± 1.6	9.9 ± 3.2	14	12.4 ± 4.8	3.2 ± 1.1	8	26.1 ± 5.9	14.9 ± 2.7
Significance[d]		$p > 0.1$	$p < 0.05$		$p > 0.5$	$p < 0.05$		$p > 0.5$	$p > 0.1$

Footnotes explained in Table 1.

<table>
<tr><td colspan="9">Reference: Wannamaker B, Morton W, Gross A, Saunders S. Improvement in Antiepileptic Drug Levels Following Reduction of Intervals Between Clinic Visits. Epilepsia 1980: 21: 155-162</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td colspan="2"></td></tr>
<tr><td></td><td></td><td></td><td></td><td>√</td><td></td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="8">To measure patient AED levels against seizure frequency to determine treatment effectiveness.</td></tr>
<tr><td>Study Design</td><td colspan="8">RCT</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="7">Outpatients from the Medical University of South Carolina Seizure Unit population who must be:
• Residents of the local community
• Actively being followed for epilepsy in clinic (Medical University of South Carolina Seizure Unit)
• On a drug regimen which was stable for 6 or more months
• Consenting by way of signature</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="7">NR</td></tr>
<tr><td>Study population Characteristics</td><td colspan="7"><table><tr><td></td><td><u>Group A</u></td><td><u>Group B</u></td></tr><tr><td>Population: (n)</td><td>14</td><td>16</td></tr><tr><td></td><td>(7 females/7 males)</td><td>(10 females/6 males)</td></tr><tr><td>Age (years)</td><td>Range: 14-50</td><td>Range: 14-52</td></tr><tr><td></td><td>Mean: 26</td><td>Mean: 29</td></tr></table></td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="7">Unclear</td></tr>
<tr><td>Methods</td><td colspan="8">• Schedules for specific times and dates for 6 monthly appointments were provided in advance to patients
• Reminders for appointments were made by telephone or correspondence
• Visits were held between 5-15 minutes and was kept at specific time
• Drug regimens were reviewed by asking the patient to name medications including specific amounts in milligrams during visits; missed medication also recorded
• Symptoms and signs of drug toxicity were sought
• Venous blood samples were drawn in the afternoon between 12 and 4 p.m. (AEDLs obtained for every visit and averaged from determinations in the 6 to 12 month period immediately preceding initiation of the monthly visits)
• New prescriptions written at each visit.
• Medications were dispensed in the clinic pharmacy (dispensing pharmacist did not give any additional information to patients)
• Average AEDLs for each drug were assigned a ranking for specified periods. (Rankings: good, fair, poor or none). See Table G-76.
• Seizure status considered improved if there was a reduction in seizure frequency ≥ 50%; seizure frequency estimated from verbal reports obtained before and during the study phase.
• Average clinic visit interval was 3.4 months; study phase was 1.1 months</td></tr>
<tr><td>Statistical Methods</td><td colspan="8">Probabilities for improvement expressed as 95% confidence intervals as shown in Table G-77.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Study quality=</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Moderate</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="8">AEDL improvements and seizure frequency measured</td></tr>
<tr><td>Results</td><td colspan="8">• Overall 19 patients (63%) showed improvement, 10 patients (33%) showed AEDL improvements, 8 patients (27%) showed seizure-status improvement and 1 patient (3%) showed improvement in both. Refer to Table G-78
• 15 of 30 patients (50%) began study with one or more AEDLs below “good” status; of the 15 patients who could have improved their AEDLs, 73% showed a positive response.
• Seizure frequency decreased or was improved in 9 patients (30%); 5 other patients reported some reduction in their seizure frequency.</td></tr>
<tr><td>Authors’ Comments</td><td colspan="8">• All patients in this study had been followed for longer than 12 months prior to the study phase and were familiar wit AEDL ascertainment as these determinations are routine on essentially every clinic visit.
• AEDLs may be used for suggesting the presence of noncompliance and for monitoring compliance, but, are minimized by author’s efforts to achieve good patient therapy and cooperation.
• When the data were analyzed for improvement in AEDL or seizure frequency or both, there was a 63.3% response to the</td></tr>
</table>

	intervention technique of this investigation. • While there was improvement, there was no correlation between increased AEDL and reduction in seizure frequency.

Table G-76 Ranking status for antiepileptic drugs µg/ml

	Good	Fair	Poor	None
Carbamazepine	> 4.0	3.9–2.5	2.4–1.5	< 1.5
Phenobarbital	> 15.0	14.9–10.0	9.9–5.0	< 5.0
Phenytoin	> 10.0	9.9–5.0	4.9–2.0	< 2.0

Table G-77. The probabilities (*p*) for improvement expressed as 95% confidence intervals

Category	Group	95% Confidence interval[a]
AEDL	A	0.083 < p < 0.580
	B	0.186 < p < 0.701
	A + B	0.195 < p < 0.539
Seizure status	A	0.083 < p < 0.580
	B	0.110 < p < 0.587
	A + B	0.136 < p < 0.464
Either or both	A + B	0.461 < p < 0.805

[a] Proportions are expressed as percentages in the text.

Table G-78. Number of patients showing improvement in AEDL, seizure status, or both following reduction in clinic visit interval.

	Improved			No change
	AEDL only	Seizure status only	Both	AEDL or seizure status
Group A n = 14	4	4	0	6
Group B n = 16	6	4	1	5
Subtotal n = 30	10	8	1	11
Total		19		11

Study Summary Tables for Key Question 6

Reference: Engelberts NHJ, Klein M, van der Ploeg HM, Heimans JJ, Jolles J, Kasteleijn-Nolst Trenite DGA. Cognition and health-related quality of life in chronic well-controlled patients with partial epilepsy on carbamazepine monotherapy. Epilepsy & Behavior 3:316-321 (2002).							
Key Questions Addressed	1	2	3	4	5	6	
						X	
Research Question	The aim of this study was to investigate whether well-controlled epilepsy individuals with late age at onset and long duration of epilepsy who have been seizure-free for more than 2 years have impaired objective neuropsychological functioning and suppressed health-related quality of life (HRQOL) and report impaired self-perceived neuropsychological functioning compared with matched healthy controls.						
Study Design	Non-randomized controlled trial						
Population	**Inclusion Criteria**	184 eligible individuals with partial epilepsy were identified from January to March 1998 from 3 outpatient clinics of the Dutch Epilepsy Clinics Foundation in The Netherlands. Medical chart audits were performed to check inclusion criteria: • Partial epilepsy • Carbamazepine (CBZ) monotherapy • 18 ≥ age ≤ 65 The eligibility criteria based on information in the medical charts were met by 148 individuals (70 of whom gave informed consent). To select well-controlled epilepsy individuals, the following criteria had to be met: • Seizure-free for at least 2 years • Epilepsy duration of at least 7 years • Epilepsy onset after completion of high school These 3 criteria excluded possible effects of confounding factors. Eventually, 16 individuals remained.					
	Exclusion Criteria	Exclusion criteria were: • Present use of psychoactive drugs or AEDs other than CBZ • Additional neurological or psychiatric disease • Severe perceptual deficits • A history of head injury, status epilepticus, neurosurgery, or neuropsychological evaluation within the last year					
	Study population Characteristics	<u>Epilepsy group</u> Mean age: 45.9 years Gender: 11 (M), 5 (F) Mean duration of epilepsy: 16 (range, 7 – 41) years Mean age at onset: 30 (range, 18 – 48) years Level of education: 5.6 IQ estimate: 115.8 <u>Healthy controls</u> Mean age: 45.5 years Gender: 11 (M), 5 (F) Level of education: 5.3 IQ estimate: 116.3					
	Generalizability to CMV drivers	Unclear					
Methods	A control group of healthy individuals was selected comparable in age, gender, and education to the epilepsy group from a large, cross-sectional study of the biological and psychological determinants of cognitive aging involving 1,940 individuals aged 25 – 80 years. An Intelligence Quotient estimate was made by means of the Dutch version of the Primary Mental Abilities test called the Groninger Intelligence Test (GIT). Three different cognitive domains were studied: • Selective Attention was indexed by the Stroop Color-Word Test (SCWT) • Verbal memory was assessed with the Auditory Verbal Learning Test (AVLT) • Retrieval from semantic memory was indexed by the Categoric Word Fluency Task Self-perceived health-related quality of life was assessed by means of the Short-Form Health Survey (SF-36). Self-perceived neuropsychological functioning was assessed using the Cognitive Failure Questionnaire (CFQ). Self-perceived mood was investigated with the Dutch short version of the POMS to measure the extent to which mood influences test scores.						

Statistical Methods	Univariate ANOVA was used to determine if objective, self-perceived neuropsychological performance and self-perceived HRQOL of the well-controlled epilepsy group differed from those of the healthy controls. To correct for multiple testing the authors restricted α to 1%. To investigate the association between overall self-perceived neuropsychological functioning investigated with the CFQ total score, objective neuropsychological functioning as indexed by Total Recall score (VVLT), card I (SCWT), Interference score (SCWT), and overall self-perceived HRQOL measured with mental compound score (MCS) and physical compound score (PCS), Pearson's correlations were calculated.													
Quality assessment	Study quality=6.8	1	2	3	4	5	6	7	8	9	10	11	12	13
		NR	NR	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N
	Moderate	14	15	16	17	18	19	20	21	22	23	24	25	
		NR	N	N	Y	Y	Y	Y	Y	Y	Y	NR	Y	
Relevant Outcomes Assessed	Rey Auditory Verbal Learning Test Stroop Test													
Results	Individuals with epilepsy did not show evidence of any difficulty with selective attention functioning (SCWT, card III). Slower information processing was found when individuals with epilepsy had to read words and name colors (SCWT, card I and card II) (see Table G-79). No problems with memory functioning were found on primary recall of newly presented information or long-term memory consolidation. Executive functioning was also not impaired.													
Authors' Comments	The present data support the assumption that individuals with well-controlled epilepsy with late age at onset and relatively long duration of epilepsy have no overall impaired HRQOL. However, when self-perceived neuropsychological functioning was investigated in detail, difficulties were reported. Lower speed of information processing was also found. Therefore, when individuals become seizure-free with adequate medication, cognition still needs to be monitored by the psychologist.													

Table G-79. Neuropsychological Test Scores and Subscales of SF-36 of Patients with Well Controlled Epilepsy and Healthy Controls

Variables	Patients with epilepsy (n = 16)	Healthy controls (n = 16)	p^b
Neuropsychological test scores			
IQ estimate			
GIT sum (nc)	115.8 ± 0.165	116.3 ± 12.2	NS
Memory (VVLT)			
Trial I (nc)	6.4 ± 1.5	6.1 ± 1.6	NS
Max (nc)	11.1 ± 2.4	12.0 ± 2.0	NS
Delta (nc)	4.7 ± 2.0	5.9 ± 2.0	NS
Total recall (nc)	44.0 ± 10.0	47.5 ± 8.3	NS
Delayed recall (nc)	9.1 ± 2.8	9.4 ± 3.3	NS
Attention (SCWT)			
Card I (s)	46.0 ± 8.6	38.7 ± 4.6	<0.008
Card II (s)	60.3 ± 10.6	49.9 ± 6.4	<0.003
Card III (s)	90.1 ± 21.0	83.4 ± 14.3	NS
Interference (s)	29.0 ± 15.6	33.4 ± 11.6	NS
Executive function			
Fluency (nc)	25.0 ± 5.8	24.4 ± 5.7	NS
HRQOL scores (SF-36)[c]			
Physical compound score (PCS)	47.8 ± 8.3	50.0 ± 9.2	NS
Mental compound score (MCS)	46.7 ± 9.4	52.7 ± 12.6	NS
Self-perceived neuropsychological functioning (CFQ)[d]			
Total score	46.2 ± 13.7	30.9 ± 11.2	<0.002

[a] See methods for explanation of abbreviations of variables. nc, Number of correct responses.
[b] Values of univariate analyses of variance (ANOVAs) between patients with epilepsy and healthy age-, gender-, and education-matched controls.
[c] Healthy controls for the SF-36 were derived from a different sample than the sample for the neuropsychological tests. Higher scores indicate better HRQOL.
[d] Higher scores indicate more problems with self-perceived neuropsychological functioning.

Reference: Hessen E, Lossius M, REinvang ZI, Gjerstad, L. Influence of Major Antiepileptic Drugs on Attention, Reaction Time, and Speed of Information Processing: Results from a randomized, Double-blind, Placebo-controlled Withdrawal Study of Seizure-free Epilepsy Patients Receiving Monotherapy. Epilepsia 47(12):2038-2045(2006).(200)														
Key Questions Addressed	1	2	3	4	5	6								
						X								
Research Question	What is the impact of discontinuation of AEDs on attention, reaction time, and speed of information processing in seizure-free individuals with epilepsy receiving monotherapy?													
Study Design	RCT													
Population	**Inclusion Criteria**	Epilepsy diagnosis (two unprovoked seizures or more) Two years of seizure freedom Monotherapy 18-67 years of age Five year seizure freedom if prior unsuccessful discontinuation												
	Exclusion Criteria	Juvenile myoclonic epilepsy (JME) Polypharmacy Paroxysmal epileptiform activity in patients with primary generalized epilepsy Two prior discontinuation attempts Pregnant or seeking pregnancy Mental retardation Progressive neurologic disease Other serious disease that may influence the health status of the patient in the study period Co-medication (except postmenopausal hormone substitution), ASA, and thyroxin												
	Study population Characteristics	No discontinuation Discontinuation N 79 71 % female 50.6 56.3 Mean age in years (range): 37.4 old (18-66) 39.2(19-65) % Epilepsy onset 0-18 yrs 41 37 % Epilepsy onset 18-60 yrs 60 63 % Seizure free 2-5 yrs 29 39 % Seizure free >5 yrs 71 62 % Known etiology 29 28 % MRI pathology 28 23 % Normal neurological status 92 94 % Carbamazepine 66 58 % Valproate 23 21 % Phenytoin 8 10 % Phenobarbitol 3 4 % Lamotrigine 1 7 % Serum Concentration within therapeutic range 82 76 % Epileptiform activity on EEG 44 35												
	Generalizability to CMV drivers	Unclear												
Methods	Potential subjects recruited from epilepsy registry at a hospital and from six neurologic outpatient clinics. 150 subjects randomized to either placebo (withdrawal) or continued on medication (no withdrawal). Subjects and investigator both blinded. Follow-up was 12 months or until seizure relapse. Neuropsychological test (California Computerized Assessment Package (CalCAP)) administered pre- and post-intervention (withdrawal/no withdrawal).													
Statistical Methods	Descriptive statistics A series of independent t-tests performed. To adjust for multiple comparisons, p<.01 required for statistical significance													
Quality assessment	Study quality=high	1	2	3	4	5	6	7	8	9	10	11	12	13

		Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NR	Y	Y
	Grade=8.2	14	15	16	17	18	19	20	21	22	23	24	25	
		N	Y	Y	Y	Y	Y	Y	N	Y	Y	NR	Y	
Relevant Outcomes Assessed	Difference in baseline to follow-up on CalCAP test scores. 10 Items on CalCAP: simple reaction time measured 3 times with dominant hand and once with the nondominant hand, choice reaction time for single digits, sequential reaction time, language discrimination, visual selective attention, response reversal and rapid visual scanning and form discrimination.													
Results	On three (choice reaction time, language discrimination, and on degraded words with distraction) of the 10 items the discontinuation group was significantly improved at follow-up compared with the no discontinuation group. A significant decrease in false-positive responses appeared in the discontinuation group on the language discrimination task. No significant changes found on other test items.													
Authors' Comments	Discontinuation of major AEDs significantly improves performance on tests that require complex cognitive processing under time pressure, as in divided attention, rapid language discrimination, and rapid form discrimination.													

Appendix H: Additional Analyses

Sensitivity Analyses for Key Question 1

Figure H-1. REMA − Includes Study of Sheth et al.

Study name	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Sheth	0.380	0.173	0.834	-2.412	0.016
Vernon	1.730	1.578	1.897	11.650	0.000
Lings	7.010	1.885	26.065	2.906	0.004
Taylor	0.910	0.761	1.088	-1.034	0.301
Hansotia	1.330	1.011	1.749	2.039	0.041
Davis	2.560	1.077	6.084	2.128	0.033
Crancer and McMurray	1.330	0.837	2.113	1.208	0.227
Waller	1.950	1.131	3.362	2.402	0.016
	1.395	1.000	1.946	1.959	0.050

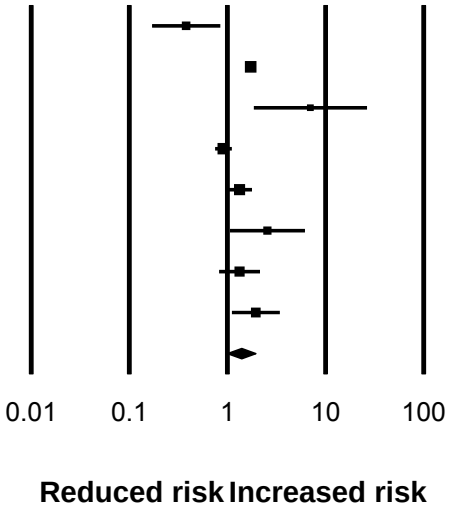


Figure H-2. REMA − Sheth et al. Excluded

Study name	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Vernon	1.730	1.578	1.897	11.650	0.000
Lings	7.010	1.885	26.065	2.906	0.004
Taylor	0.910	0.761	1.088	-1.034	0.301
Hansotia	1.330	1.011	1.749	2.039	0.041
Davis	2.560	1.077	6.084	2.128	0.033
Crancer and McMurray	1.330	0.837	2.113	1.208	0.227
Waller	1.950	1.131	3.362	2.402	0.016
	1.565	1.133	2.161	2.720	0.007

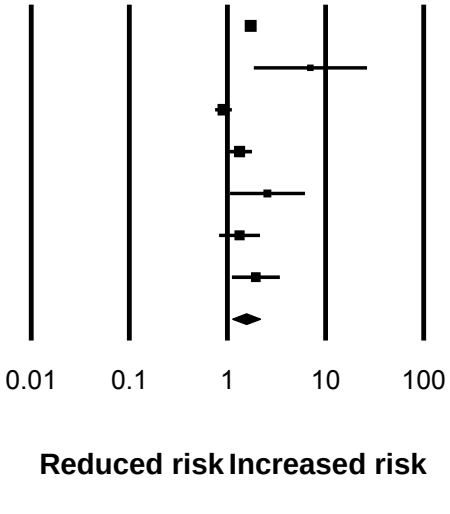


Figure H-3. REMA − One Study Removed at a Time

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Vernon	1.534	1.059	2.223	2.260	0.024
Lings	1.449	1.054	1.991	2.285	0.022
Taylor	1.675	1.341	2.093	4.542	0.000
Hansotia	1.661	1.119	2.466	2.516	0.012
Davis	1.497	1.067	2.102	2.334	0.020
Crancer and McMurray	1.624	1.129	2.338	2.612	0.009
Waller	1.521	1.066	2.171	2.313	0.021
	1.565	1.133	2.161	2.720	0.007

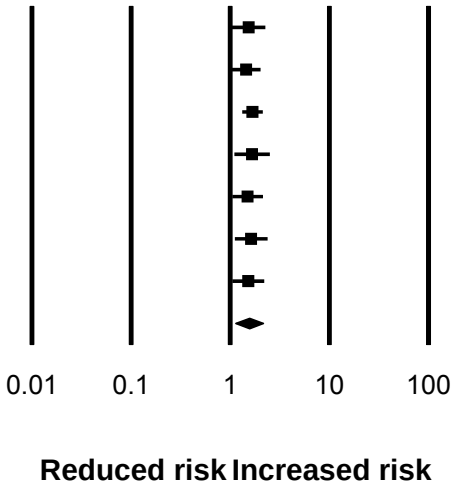


Figure H-4. REMA − Cumulative Meta Analysis 1: Most Recent Study First

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Vernon	1.730	1.578	1.897	11.650	0.000
Lings	2.969	0.781	11.281	1.597	0.110
Taylor	1.613	0.879	2.960	1.542	0.123
Hansotia	1.479	0.952	2.297	1.741	0.082
Davis	1.582	1.051	2.380	2.199	0.028
Crancer and McMurray	1.521	1.066	2.171	2.313	0.021
Waller	1.565	1.133	2.161	2.720	0.007
	1.565	1.133	2.161	2.720	0.007

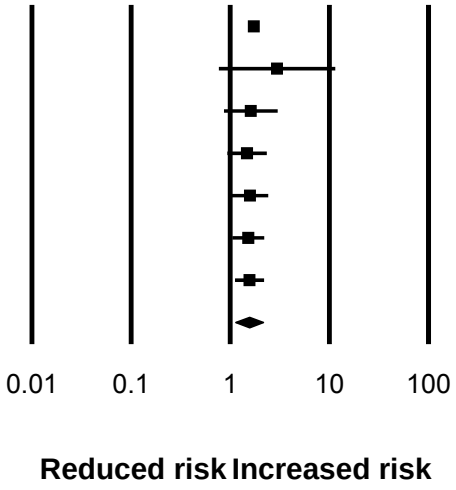


Figure H-5. REMA − Cumulative Meta Analysis 2: Oldest Study First

Study name	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Waller	1.950	1.131	3.362	2.402	0.016
Crancer and McMurray	1.566	1.081	2.269	2.369	0.018
Davis	1.688	1.196	2.384	2.977	0.003
Hansotia	1.482	1.178	1.866	3.352	0.001
Taylor	1.355	0.979	1.875	1.833	0.067
Lings	1.534	1.059	2.223	2.260	0.024
Vernon	1.565	1.133	2.161	2.720	0.007
	1.565	1.133	2.161	2.720	0.007

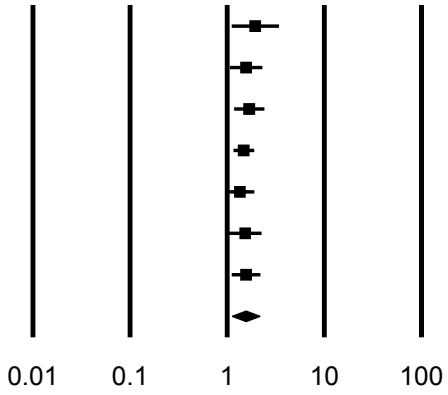
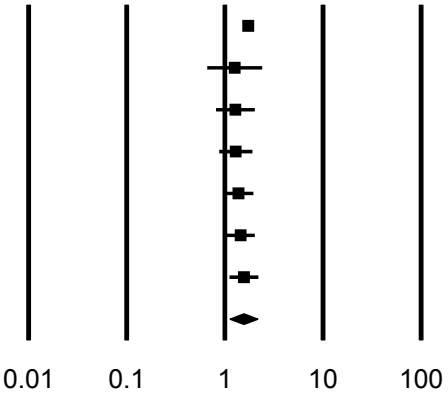


Figure H-6. REMA − Cumulative Meta Analysis 3: Highest Weighted Study First

Study name	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Vernon	1.730	1.578	1.897	11.650	0.000
Taylor	1.261	0.672	2.366	0.721	0.471
Hansotia	1.284	0.827	1.993	1.112	0.266
Crancer and McMurray	1.293	0.891	1.877	1.352	0.176
Waller	1.375	0.984	1.920	1.868	0.062
Davis	1.449	1.054	1.991	2.285	0.022
Lings	1.565	1.133	2.161	2.720	0.007
	1.565	1.133	2.161	2.720	0.007



Sensitivity Analyses for Key Question 3

Figure H-7 REMA − One Study Removed at a Time

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Jeha	0.409	0.072	0.005	0.268	0.549	5.689	0.000
Kelly	0.335	0.064	0.004	0.209	0.461	5.205	0.000
Spencer	0.409	0.072	0.005	0.267	0.550	5.663	0.000
McIntosh	0.476	0.087	0.008	0.305	0.648	5.448	0.000
Yoon	0.437	0.075	0.006	0.289	0.585	5.787	0.000
Jutila	0.370	0.066	0.004	0.241	0.498	5.620	0.000
Salanova	0.353	0.067	0.004	0.223	0.484	5.296	0.000
So	0.386	0.067	0.005	0.254	0.517	5.745	0.000
Eliashiv	0.486	0.099	0.010	0.292	0.681	4.901	0.000
Foldvary	0.379	0.067	0.005	0.248	0.511	5.655	0.000
Rougier	0.365	0.067	0.005	0.233	0.497	5.422	0.000
	0.396	0.068	0.005	0.263	0.528	5.852	0.000

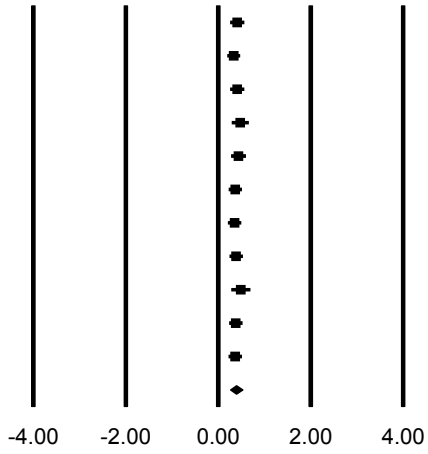


Figure H-8. REMA − Cumulative Meta Analysis 1: Newest Study First

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Jeha	0.291	0.126	0.016	0.043	0.539	2.300	0.021
Kelly	0.514	0.214	0.046	0.094	0.934	2.399	0.016
Spencer	0.445	0.153	0.023	0.146	0.744	2.918	0.004
McIntosh	0.346	0.162	0.026	0.029	0.663	2.141	0.032
Yoon	0.305	0.106	0.011	0.097	0.513	2.870	0.004
Jutila	0.330	0.099	0.010	0.135	0.525	3.324	0.001
Salanova	0.394	0.099	0.010	0.199	0.589	3.958	0.000
So	0.413	0.100	0.010	0.217	0.610	4.126	0.000
Eliashiv	0.349	0.067	0.004	0.218	0.480	5.229	0.000
Foldvary	0.365	0.067	0.005	0.233	0.497	5.422	0.000
Rougier	0.396	0.068	0.005	0.263	0.528	5.852	0.000
	0.396	0.068	0.005	0.263	0.528	5.852	0.000

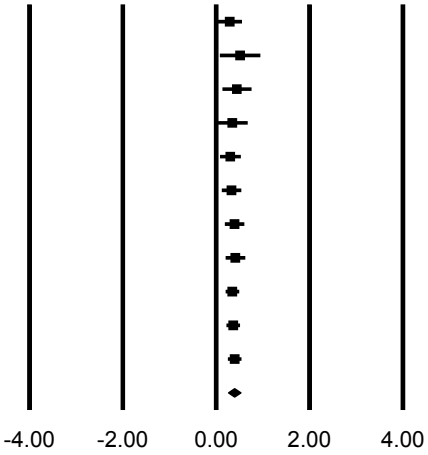


Figure H-9. REMA − Cumulative Meta Analysis 2: Oldest Study First

Study name	Cumulative statistics						
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Rougier	1.030	0.280	0.078	0.482	1.578	3.682	0.000
Foldvary	1.127	0.252	0.063	0.634	1.620	4.479	0.000
Eliashiv	0.787	0.420	0.176	-0.036	1.610	1.875	0.061
So	0.972	0.419	0.176	0.151	1.793	2.320	0.020
Salanova	0.963	0.338	0.114	0.301	1.625	2.850	0.004
Jutila	0.623	0.138	0.019	0.352	0.894	4.503	0.000
Yoon	0.484	0.107	0.011	0.275	0.693	4.537	0.000
McIntosh	0.350	0.074	0.006	0.204	0.495	4.714	0.000
Spencer	0.342	0.069	0.005	0.207	0.476	4.979	0.000
Kelly	0.409	0.072	0.005	0.268	0.549	5.689	0.000
Jeha	0.396	0.068	0.005	0.263	0.528	5.852	0.000
	0.396	0.068	0.005	0.263	0.528	5.852	0.000

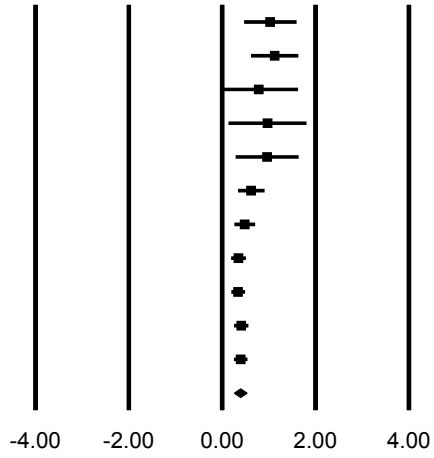
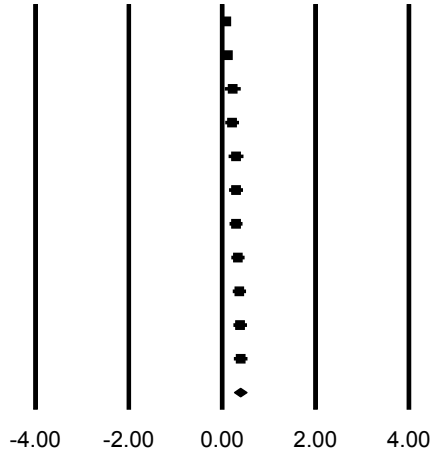


Figure H-10. REMA − Cumulative Meta Analysis 3: Highest Weighted Study First

Study name	Cumulative statistics						
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
McIntosh	0.090	0.018	0.000	0.055	0.125	5.102	0.000
Eliashiv	0.124	0.035	0.001	0.055	0.192	3.541	0.000
Jutila	0.226	0.080	0.006	0.068	0.383	2.807	0.005
Yoon	0.213	0.067	0.005	0.081	0.345	3.174	0.002
Kelly	0.297	0.074	0.006	0.152	0.443	3.995	0.000
Spencer	0.297	0.069	0.005	0.162	0.432	4.319	0.000
Jeha	0.297	0.065	0.004	0.170	0.423	4.591	0.000
Salanova	0.339	0.066	0.004	0.209	0.468	5.131	0.000
Rougier	0.369	0.067	0.004	0.239	0.500	5.552	0.000
Foldvary	0.386	0.067	0.005	0.254	0.517	5.745	0.000
So	0.396	0.068	0.005	0.263	0.528	5.852	0.000
	0.396	0.068	0.005	0.263	0.528	5.852	0.000



Sensitivity Analyses for Key Question 4

Figure H-11. REMA − One Study Removed at a Time

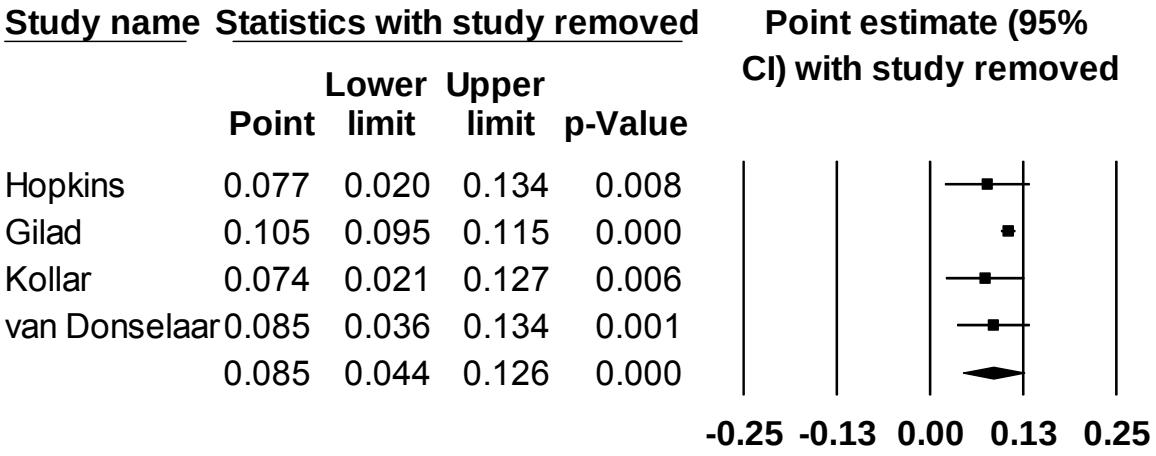


Figure H-12. REMA − Cumulative Meta Analysis 1: Newest Study First

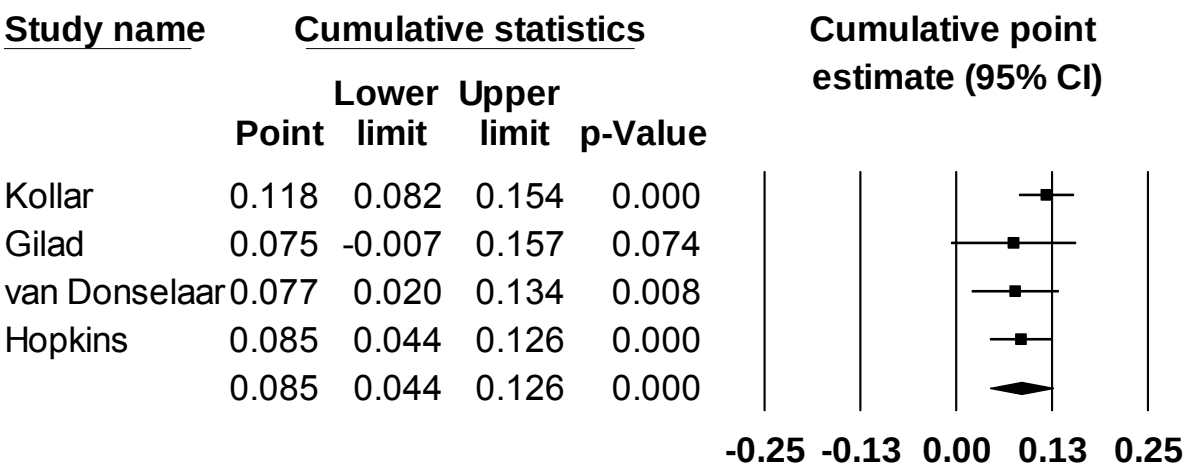


Figure H-13. REMA − Cumulative Meta Analysis 2: Oldest Study First

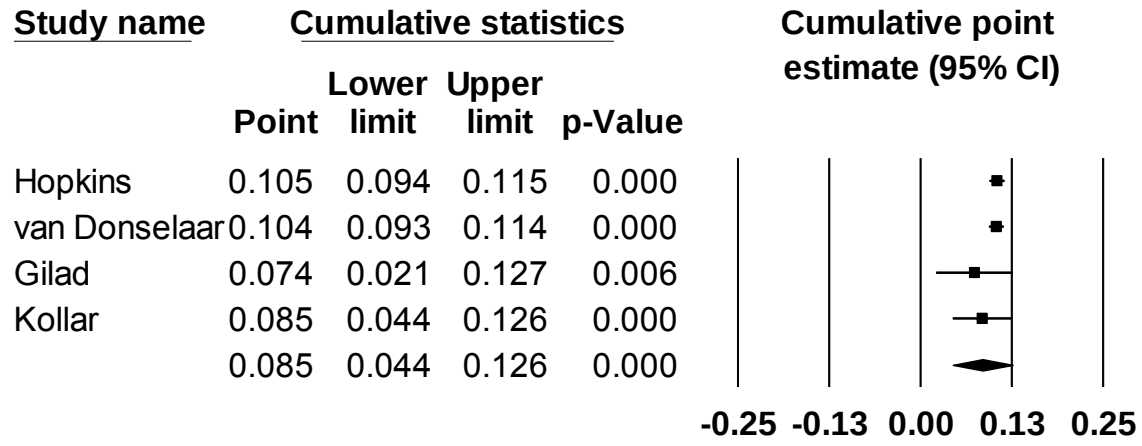


Figure H-14. REMA − Cumulative Meta Analysis 3: Highest Weighted Study First