Executive Summary:
Seizure Disorders and Commercial Motor Vehicle Driver Safety

Presented to

Federal Motor Carrier Safety Administration

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Prepared for

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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.

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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.

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, 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

[1] >2 weeks treatment

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.