Seizure Disorder and Medical Certification of Commercial Motor Vehicle Driver Safety

Evidence Report and Systematic Review

Prepared for the Federal Motor Carrier Safety Administration
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Executive Summary

Introduction

Driving a large commercial motor vehicle is dangerous work. In 2016, the Federal Motor Carrier Safety Administration (FMCSA) found that "4,440 large trucks and buses were involved in fatal crashes, a 2-percent increase from 2015".[1] In 2017, the Bureau of Labor Statistics (BLS) reported that truck drivers and delivery workers had the highest number of workplace fatalities (840), and that this "represented the highest value for heavy and tractor-trailer truck drivers" since reporting on those job types began in 2003.[2]

FMCSA's primary mission is to reduce the number of crashes, injuries, and fatalities suffered by commercial motor vehicle (CMV) operators. FMCSA's Medical Programs Division supports this mission by working to ensure that CMV drivers involved in interstate commerce are physically qualified and able to safely perform their work. As part of the effort to improve safety, the FMCSA periodically commissions systematic reviews of the scientific literature related to a variety of topics relevant to safe CMV operations. The results of these studies, combined with input from the FMCSA's Medical Expert Panel, are used to inform agency decision-making and policy updates.

This report considers the impact of seizure disorders on the risk of motor vehicle accidents, how indirect measures of driving ability are impacted by seizures, and the effectiveness of medications and resective surgeries in controlling seizures. Evidence of the relationship between seizure disorder and motor vehicle crash risk published since 2007 is assessed and summarized. The results reported are principally derived from studies that do not involve CMV drivers, as little research has been conducted on seizure disorders and epilepsy as it impacts crash risks among CMV operators.

The National Highway Transportation Safety Administration's (NHTSA) annual Fatality Analysis Reporting census reported 722 *truckers killed* in traffic *crashes* in 2016, up 8.6 percent from the prior year.[3] There are, however, few studies of seizures or epilepsy as causes of accidents among commercial drivers, and the data on risks are derived principally from studies involving noncommercial drivers.

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[1] U.S. Department of Transportation/Federal Motor Carrier Safety Administration/Analysis Division. Large Truck and Bus Crash Facts 2016. Retrieved from: https://www.fmcsa.dot.gov/safety/data-and-statistics/large-truck-and-bus-crash-facts-2016

[2] U.S. Department of Labor/Bureau of Labor Statistics. News Release: National Census of Fatal Occupational Injuries in 2017. Retrieved from: https://www.bls.gov/news.release/pdf/cfoi.pdf

[3] U.S. Department of Transportation/National Highway Traffic Safety Administration. (2017). Traffic Safety Facts; Research Note; 2016 Fatal Motor Vehicle Crashes: Overview. Retrieved from: https://www.fmcsa.dot.gov/safety/data-and-statistics/large-truck-and-bus-crash-facts-2016; https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/812456

Research Questions

FMCSA has identified the following research questions for this study:

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?**
2. **What is the relationship between seizure recurrence likelihood and the time since last seizure among individuals who are on anti-epileptic drug (AED) treatment and are apparently seizure free?**
3. **What is the relationship between seizure recurrence likelihood and the time since last seizure among individuals who have undergone resective surgery and are apparently seizure free?**
4. **What is the relationship between seizure recurrence likelihood and the time since last seizure among individuals who have experienced a single unprovoked seizure?**
5. **What is the relationship between compliance with a prescribed anti-epileptic drug (AED) treatment (as measured by drug serum levels) and the effectiveness of that treatment in preventing seizure recurrence?**
6. **What are the chronic effects of an AED on surrogate markers of driver safety among individuals with recurrent seizure disorders?**

Search Methodology

We searched thousands of peer-reviewed journals using precisely defined key search terms to locate materials for this study. We searched the following electronic databases:

The Cochrane Library, including:

- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials
- Cochrane Methodology Register
- Database of Abstracts of Reviews of Effects
- Health Technology Assessment Database
- NHS Economic Evaluation Database
- Cumulative Index to Nursing & Allied Health (CINAHL)
- Embase (Excepta Medica)
- PsycINFO
- PubMed: The National Library of Medicine's MEDLINE and PreMEDLINE databases
- Transportation Research Information Service Database (TRIS)

In addition, we also searched for unpublished reports, studies, and other materials on Web sites of Federal agencies, as well as related commercial and non-profit organizations, for studies which are not commercially available. Finally, we reviewed the references of retrieved articles to locate any additional relevant materials.

Findings

Research 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?

The evidence base for Question 1 consists of ten studies. Most of the studies found associations between seizures and motor vehicle crashes, indicating it is likely that individuals with recurrent seizure disorders (epilepsy) are at an increased risk for a motor vehicle crash when they are driving compared to non-epileptic individuals. However, it is difficult to estimate the magnitude of this increased risk because the associations are not strong and the studies themselves tend to be contradictory.

All ten studies present data on the risk of crashes experienced by individuals with epilepsy, but only two of the studies contained comparison groups of individuals who lacked the disorder. Seven of the studies found evidence of an increased risk associated with epilepsy. One study had inconsistent findings, and two studies found that crash risk was no higher than in the general population. **There is moderate evidence to support the contention that individuals with recurrent seizure disorders (epilepsy) are at an increased risk for a motor vehicle crash as compared to comparable individuals who do not have a seizure disorder.**

Research Question 2

What is the relationship between seizure recurrence likelihood and the time since last seizure among individuals who are on anti-epileptic drug (AED) treatment and are apparently seizure free?

The evidence base identified for Question 2 includes 33 studies. The majority of these studies found an inverse relationship between the likelihood of seizure recurrence and the time since last seizure (TSLS) among individuals who were receiving AED treatment. Twenty seven of these 33 articles reported that, with various AED treatments, the likelihood of seizure recurrence is reduced and TSLS is increased. However, few of these studies included control groups and the results generally describe association rather than causation. In addition, many of the articles described treatment with different specific drugs.

The majority of evidence reviewed here studying individuals treated with AEDs supports an inverse relationship between the likelihood of seizure recurrence and the TSLS. As a result of

these studies, it is difficult to compare effectiveness of AED treatment across drugs. It seems many of the drugs are somewhat effective in treating seizures, and that the differences in response may lie in the type and severity of an individual's seizure disorder. **There is moderate evidence of an association between the likelihood of seizure recurrence and TSLS among individuals who are on an AED and are seemingly free of seizures.**

Research Question 3

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

No articles that met the inclusion criteria for this question were found.

Research 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?

Only one original research article was uncovered for the Question 4 evidence base. This single qualifying study found that the relationship between seizure recurrence and time since last seizure could be increased by 2.2 months with carbamazepine treatment. Possible risks for bias may have been introduced due to allocation concealment since randomization methods were unclear, as well
as performance and detection bias due to lack of blinding. However, the inclusion of a control group limited the effect of these potential biases. **There is unacceptably weak evidence regarding the likelihood of seizure recurrence among individuals who have experienced a single unprovoked seizure.**

Research Question 5

What is the relationship between compliance with a prescribed anti-epileptic drug (AED) treatment (as measured by drug serum levels) and the effectiveness of that treatment in preventing seizure recurrence?

No articles that met the inclusion criteria for this question were found.

Research Question 6

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

The evidence base for Question 6 consists of eight studies. All of the studies included in the evidence base for this Research Question assessed the impact of AEDs on cognitive functions that can be used as surrogate measures of driving performance. Of these, two included measurement and assessment of AED use on driving performance using a driving simulator. There was little agreement between or among the study findings, with some studies observing cognitive impairment linked to AED use and others observing that AEDs were

linked to improvement to, or maintenance of, cognitive function. This may be partly explained by the differing designs, methods, and goals of the various studies. **The evidence base regarding the chronic effect of AED treatment on surrogate markers of driver safety is unacceptably weak.**

Preface

Introduction

There are approximately 3.5 million professional truck drivers in the United States.[4] In 2016, the Federal Motor Carrier Safety Administration (FMCSA) found that "4,440 large trucks and buses were involved in fatal crashes, a 2-percent increase from 2015."[5] In 2017, the Bureau of Labor Statistics (BLS) reported that truck drivers and delivery workers had the highest number of workplace fatalities (840), and that this "represented the highest value for heavy and tractor-trailer truck drivers" since reporting on those job types began in 2003.[6]

FMCSA's primary mission is to reduce the number of crashes, injuries, and fatalities suffered by commercial motor vehicle (CMV) operators. FMCSA's Medical Programs Division supports this mission by working to ensure that CMV drivers involved in interstate commerce are physically qualified and able to perform their work safely. As part of the effort to improve safety, the FMCSA periodically commissions systematic reviews of the scientific literature related to a variety of medical topics relevant to safe CMV operations. The results of these studies, combined with input from the FMCSA's Medical Expert Panel, are used to inform agency decision-making and policy updates.

This report considers the impact of seizure disorders on the risk of motor vehicle accidents, how indirect measures of driving ability are impacted by seizures, and the effectiveness of medications and resective surgeries in controlling seizures. Evidence of the relationship between seizure disorder and motor vehicle crash risk published since 2007 is assessed and summarized.

There are, however, few studies of seizures or epilepsy as causes of accidents among commercial drivers, and the data on risks are derived principally from studies involving noncommercial drivers. One study conducted using traffic records from the Netherlands indicated that 1 traffic accident per 10,000 is caused by a seizure at the wheel. This compares to 6 per 10,000 caused by natural death at the wheel and 5,000 per 10,000 caused by alcohol.

[4] American Trucking Association. (2016). Reports, Trends & Statistics. Retrieved from: https://www.trucking.org/News_and_Information_Reports_Industry_Data.aspx

[5] U.S. Department of Transportation/Federal Motor Carrier Safety Administration/Analysis Division. Large Truck and Bus Crash Facts 2016. Retrieved from: https://www.fmcsa.dot.gov/safety/data-and-statistics/large-truck-and-bus-crash-facts-2016

[6] U.S. Department of Labor/Bureau of Labor Statistics. News Release: National Census of Fatal Occupational Injuries in 2017. Retrieved from: https://www.bls.gov/news.release/pdf/cfoi.pdf

Although the risk for accidents caused by seizures is small, it has been estimated that the accident rate for people with epilepsy is approximately twice that of the population at large.[7]

Epilepsy is the most common serious neurological disorder, affecting approximately 50 million people worldwide.[8]

Noncommercial drivers with epilepsy are between 1.13 and 2.16 times more likely to experience a motor vehicle crash than comparable drivers who do not have the disorder.[9]

Under the standards that govern suitability for a commercial driver's license (49 CFR § 391.41) a person cannot operate a commercial motor vehicle if they have an "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."[10]

Based on current the current guidelines developed by the FMCSA Medical Expert Panel (MEP) in 2007, conditional certification for individuals with epilepsy may be granted in some instances. An individual may obtain conditional certification to operate a CMV (or maintain a certification under a conditional status) under the following criteria[11]:

- *Individual must have been seizure free for a minimum of 8 years on or off anti-seizure medication; AND*
    - *If all anti-seizure medications have been stopped, the individual must have been seizure free for a minimum of 8 years from the time of medication cessation; OR*
    - *If still using anti-seizure medication, the individual must have been on a stable medication regimen for a minimum of 2 years.*

Similar guidelines exist for individuals who have experienced a history of provoked seizures, as well as those who have experienced a single unprovoked seizure (in the case of the latter group, the 8 years required for seizure freedom or from cessation of anti-seizure drugs is reduced to 4 years).

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[7] U.S. Department of Transportation/Federal Motor Carrier Safety Administration. Seizures, Epilepsy, and Interstate Commercial Driving. Retrieved from https://www.fmcsa.dot.gov/sites/fmcsa.dot.gov/files/docs/neuro2.pdf

[8] Aydemir, N., Trung, D.V., Snape, D., Baker, G.A., Jacoby, A. (2009). Multiple impacts of epilepsy and contributing factors: findings from an ethnographic study in Vietnam. *Epilepsy Behavior: 16*:512–20.

[9] ECRI, & MANILA Consulting Group. (2007, November 30). Evidence report: Seizure disorders and commercial motor vehicle driver safety (Comprehensive review). Federal Motor Carrier Safety Administration.

[10] Qualifications of drivers and longer combination vehicle (LCV) driver instructors, 49 CFR § 391.41. Retrieved from https://www.ecfr.gov/cgi-bin/text-idx?rgn=div5&node=49:5.1.1.2.34#se49.5.391_141

[11] ECRI, & MANILA Consulting Group. (2007, October 15). Expert panel recommendations: Seizure disorders and commercial motor vehicle driver safety. Federal Motor Carrier Safety Administration.

FMCSA began granting exemptions, renewable every two years, in 2013, and has granted 343 as of 2018.

The National Highway Transportation Safety Administration's (NHTSA) annual Fatality Analysis Reporting census reported 722 *truckers killed* in traffic *crashes* in 2016, up 8.6 percent from the prior year.[12] There are, however, few studies of seizures or epilepsy as causes of accidents among commercial drivers, and the data on risks are derived principally from studies involving noncommercial drivers.

Purpose of Report

In 2018, the FMCSA contracted with Acclaro Research Solutions, Inc. (Acclaro) to update the 2007 Evidence Report on Seizure Disorder and Commercial Motor Vehicle Driver Safety by completing an exhaustive literature review analyzing the impact of seizure disorders on commercial motor vehicle safety. This effort serves to update the findings or the previous review, completed in 2007 by Manila Consulting Group, Inc. and ECRI. The current report uses the same six Research Questions used in 2007. This report summarizes recent studies from the published, professional research literature, while answering the research questions.

This report addresses the following research questions:

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?**
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3. **What is the relationship between seizure recurrence likelihood and the time since last seizure among individuals who have undergone resective surgery and are apparently seizure free?**
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6. **What are the chronic effects of an AED on surrogate markers of driver safety among individuals with recurrent seizure disorders?**

[12] U.S. Department of Transportation/National Highway Traffic Safety Administration. (2017). Traffic Safety Facts; Research Note; 2016 Fatal Motor Vehicle Crashes: Overview. Retrieved from: https://www.fmcsa.dot.gov/safety/data-and-statistics/large-truck-and-bus-crash-facts-2016; https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/812456

Report Organization

This evidence report and systematic review contains three major sections:

1. Background information on epilepsy and seizures
2. Methodology
3. Evidence Summary

The Background section briefly reviews pertinent information about seizures. Topics addressed include brief discussion of epilepsy and seizures, types of seizures, seizure triggers, and common treatments.

The Methodology section provides a detailed description of the sources searched as part of this effort, the search terms utilized for each research question and how the research term determined which resources should be included in the evidence base. Finally, this section describes the approach used to determine the quality of the evidence for each research question.

Finally, the Evidence Summary provides a thorough description of the evidence base for each research question and includes summaries for each study included organized by research question.

Report Funding and Role of Funders

This review was funded via contract DTMC75-13-R-00025 from FMCSA. FMCSA reviewed the report and provided comments. However, all research was conducted independently by Acclaro Research Solutions, Inc. and all findings are our own.

All authors declare no financial or other conflicts of interest.

Background

What is Epilepsy?

Epilepsy is a chronic neurological disorder that is fundamentally characterized by recurrent, unprovoked seizures. Affecting people of all ages, epilepsy affects approximately 50 million people around the world, according to the World Health Organization, with 2.4 million new diagnoses each year worldwide.[13] The most recent statistics provided by the Centers for Disease Control and Prevention indicate that in 2015, approximately 3.4 million Americans live with epilepsy, representing about 1.2% of the total U.S. population.[14]
Based on the traditional definition, a person can be diagnosed with epilepsy following two unprovoked seizures more than 24 hours apart.[15]

The International League Against Epilepsy (ILAE) proposed an expanded definition in 2014, indicating that one or more of the following conditions define epilepsy[16]:

1. At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
3. Diagnosis of an epilepsy syndrome
    - Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years with no seizure medicines for the last 5 years.

Note that according the ILAE[17]:

> *Item 3 refers to epilepsy syndromes such as benign epilepsy with central-temporal spikes, previously known as benign rolandic epilepsy, which is usually outgrown by age 16 and always by age 21. If a person is past the age of the syndrome, then epilepsy is resolved. If a person has been seizure-free for at least 10 years with the most recent 5 years off all*

[13] World Health Organization. (2018, February 8). Epilepsy. Retrieved from https://www.who.int/news-room/fact-sheets/detail/epilepsy
[14] Centers for Disease Control and Prevention. (2018, July 31). Epilepsy fast facts. Retrieved from https://www.cdc.gov/epilepsy/about/fast-facts.htm
[15] Fisher, R.S. (2014, April 15). Epilepsy: A new definition. Retrieved from https://www.epilepsy.com/article/2014/4/revised-definition-epilepsy
[16] Ibid.
[17] Fisher, R.S. (2014, April 15) The 2014 Definition of Epilepsy: A perspective for patients and caregivers. Retrieved from https://www.ilae.org/guidelines/definition-and-classification/the-2014-definition-of-epilepsy-a-perspective-for-patients-and-caregivers

anti-seizure medications, then their epilepsy also may be considered resolved. Being resolved does not guarantee that epilepsy will not return, but it means the chances are small and the person has a right to consider that she or he is free from epilepsy.

There are many different types of epilepsy—hundreds of epilepsy disorders, each with its own symptoms—have been identified.[18] While some instances of epilepsy can be linked to an occurrence of injury to the brain or to inherited family traits, most cases of epilepsy have no known cause.[19] Frequently, epilepsy syndromes are described by where they originate in the brain and their associated symptoms. Common epilepsy syndromes include:[20]

- Absence epilepsy – Repeated seizures cause lapses in consciousness, often characterized by unfocused staring. Physical symptoms may also include rapid eye blinking and muscle jerking.
- Frontal lobe epilepsy – Brief, clustered seizures occurring in the areas of the brain responsible for movement. Seizures can cause a loss of awareness, as well as physical symptoms such as unusual, uncontrolled movement of the muscles.
- Temporal lobe epilepsy – Seizures occurring in one of the brain's temporal lobes. These seizures are characterized by lapses in consciousness or awareness and involuntary movements; they are often immediately preceded by symptoms such as nausea, feelings of unease or déjà vu, and unusual smells or tastes.
- Neocortical epilepsy – Seizures occurring in the outer layer of the brain. Symptoms include contractions or convulsions in the muscles, unusual sensory perception, changes in emotion, and hallucinations.

What is a Seizure?

A seizure is the result of abnormal, sudden, or excessive electrical activity in one or more parts of the brain. There are a variety of types of seizure, defined by where they occur in the brain and what effects they have on the body.

Terminology for seizures has varied, with classifications further refined and expanded as understanding of seizures has increased. Seizures are characterized by where they occur within in the brain, and further characterized by their effects; the CDC classifies seizures in two groups:[21]

1. Generalized seizures: occur in both sides of the brain

[18] National Institute of Neurological Disorders and Stroke. (2015, April). Epilepsy: Hope through research. Retrieved from https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Epilepsies-and-Seizures-Hope-Through#3109_29

[19] Centers for Disease Control and Prevention. (2019, January 4). What causes epilepsy? Retrieved from https://www.cdc.gov/epilepsy/about/faq.htm#What%20causes%20epilepsy?

[20] National Institute of Neurological Disorders and Stroke. (2015, April). Epilepsy: Hope through research. Retrieved from https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Epilepsies-and-Seizures-Hope-Through#3109_29

[21] Centers for Disease Control and Prevention. (2018, January 17). Types of Seizures. Retrieved from https://www.cdc.gov/epilepsy/about/types-of-seizures.htm

    - Absence seizures: also known as petit mal, absence seizures are commonly characterized by staring or rapid blinking of the eyes
    - Tonic-clonic seizures: also known as grand mal, tonic-clonic seizures can cause loss of consciousness, muscle spasms or jerking, falling, or crying out
2. Focal seizures: also known as partial onset, these seizures begin in one side of the brain, but can expand to both sides; focal onset seizures can be classified in one of the following ways:
    - Simple focal seizures: also known as a simple partial seizure, these seizures can be characterized by twitching of the muscles and perception of strange or unusual tastes or smells
    - Complex focal seizures: also known as a complex partial seizure, these seizures are characterized by confusion or other impairment to awareness
    - Secondary generalized seizures: these seizures begin as focal seizures in one part of the brain before becoming generalized seizures occurring across both hemispheres

Within each of these types, seizures can present many different types of symptoms, which are categorized as either motor or non-motor. A person with epilepsy can experience more than one of the seizure types.[22]

Motor symptoms associated with seizures are described by one or more of the following characteristics[23]:

- Tonic – stiffening of the muscles
- Atonic – relaxation of the muscles
- Myoclonic – short, uncontrolled jerking in parts of the body
- Clonic – sustained periods of uncontrolled jerking or shaking in parts of the body

Non-motor symptoms do not involve movement and are instead reflected by changes in cognition, sensory perception, attention, or consciousness; they can also be characterized by a lack of movement.

Seizure Triggers

People who experience seizures may be able link a seizure's onset to a specific activity, time of day, sensory input, behavior, or physical condition; factors that precede a seizure are known as seizure triggers. Epilepsy in which seizures occur as a direct response to specific triggers is known as reflex epilepsy; photosensitive epilepsy, in which a seizure is triggered by flashing

[22] Centers for Disease Control and Prevention. (2018, January 17). Types of seizures. Retrieved from https://www.cdc.gov/epilepsy/about/types-of-seizures.htm
[23] Ibid.

light, is among the most well-known and most common type of reflex epilepsy,[24] though it only effects approximately 3% of the total number of people with epilepsy.[25,26]

Epilepsy Treatment

There is no prevention for epilepsy, though it can be treated and managed.[27] The most common treatment for epilepsy is through anti-seizure drugs, also known as antiepileptic drugs (AEDs). There are over 20 anti-seizure drugs currently available, offering different benefits and carrying different side effects, though most side effects are relatively minor and can include dizziness and fatigue.[28] The National Institute of Neurological Disorders and Stroke (NINDS) notes that the drug and dose prescribed for an individual with epilepsy "depends on many different factors, including seizure type, lifestyle and age, seizure frequency, drug side effects, medicines for other conditions, and, for a woman, whether she is pregnant or will become pregnant."[29]

For many, seizures can be controlled by using a single drug, known as monotherapy, though others may require the addition of one or more drugs.

When anti-seizure drugs are not effective in stopping seizures, other treatment options include surgery to remove the areas of the brain that are producing the seizures; stimulation of the vagus nerve, to send short bursts of electrical energy directly into the brain; a ketogenic diet, which is high in fats and low in carbohydrates[30]; and complementary and alternative therapies[31].

Evaluation for surgery, according to the NINDS, "is generally recommended only after focal seizures persist despite the person having tried at least two appropriately chosen and well-tolerated medications, or if there is an identifiable brain lesion (a dysfunctional part of the brain) believed to cause the seizures."[32]

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[24] Holmes, G.L., Fisher, R.S. (2013, September). Reflex epilepsies. Retrieved from https://www.epilepsy.com/learn/types-epilepsy-syndromes/reflex-epilepsies

[25] Shafer, P.O., Sirven, J.I. (2018, November 18). Photosensitivity and seizures. Retrieved from https://www.epilepsy.com/learn/triggers-seizures/photosensitivity-and-seizures

[26] Epilepsy Society. (2016, October). Photosensitive epilepsy. Retrieved from https://www.epilepsysociety.org.uk/photosensitive-epilepsy#.XEIUCVxKguU

[27] National Institute of Neurological Disorders and Stroke. (2015, April). Epilepsy: Hope through research. Retrieved from https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Epilepsies-and-Seizures-Hope-Through#3109_29

[28] Ibid.

[29] Ibid.

[30] Center for Parent Information and Resources. (2015, June). *Epilepsy* Fact Sheet. Retrieved from https://www.parentcenterhub.org/epilepsy/

[31] Epilepsy Foundation. (2018). Treating Seizures and Epilepsy - Complementary Health Approaches. Retrieved from https://www.epilepsy.com/learn/treating-seizures-and-epilepsy/complementary-health-approaches

[32] National Institute of Neurological Disorders and Stroke. (2015, April). Epilepsy: Hope through research. Retrieved from https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Epilepsies-and-Seizures-Hope-Through#3109_29

Research Methodology and Evidence Base

Sources Searched

We searched thousands of peer-reviewed journals using precisely defined key search terms to locate materials for this study. We searched the following electronic databases:

- **The Cochrane Library:** This is a collection of six databases that contain high-quality information to inform healthcare decision-making, including:
  - Cochrane Database of Systematic Reviews
  - Cochrane Central Register of Controlled Trials
  - Cochrane Methodology Register
  - Database of Abstracts of Reviews of Effects
  - Health Technology Assessment Database
  - NHS Economic Evaluation Database
- **Cumulative Index to Nursing & Allied Health (CINAHL):** Over 700 journals on topics related to nursing and allied health
- **Embase (Excepta Medica):** An index to pharmacological and biomedical literature from over 6,500 journals from 70 countries, including most MEDLINE records
- **PsycINFO**: Over 2,500 journals covering psychology and its related fields
- **PubMed**: The National Library of Medicine's MEDLINE and PreMEDLINE databases; MEDLINE encompasses information from Index Medicus, Index to Dental Literature, and International Nursing Index, as well as other sources of coverage in the areas of allied health, biological and physical sciences, humanities and information science as they relate to medicine and health care
- **Transportation Research Information Service Database (TRIS)**: More than one million records related to worldwide transportation research

In addition, we also searched the "grey literature," which consists of unpublished reports, studies, and other materials which are not commercially available. We sought out these materials by searching the Web sites of various Federal agencies, as well as related commercial and non-profit organizations. We searched:

- American Association of Pharmaceutical Scientists (AAPS) http://www.aaps.org/PharmRes/
- American College of Occupational and Environmental Medicine http://www.acoem.org/default.aspx
- American Society of Health-System Pharmacists http://www.ashp.org/
- American Trucking Association http://www.truckline.com/
- Commercial Vehicle Safety Alliance http://www.cvsa.org/home.php

- DOT Bureau of Transportation Statistics http://www.rita.dot.gov/bts/
- Federal Motor Carrier Safety Administration http://fmcsa.dot.gov/
- Food and Drug Administration http://www.fda.gov/
- International Pharmaceutical Federation (FIP) http://fip.org/
- National Transportation Safety Board http://www.ntsb.gov/
- PhRMA, the Pharmaceutical Research and Manufacturers of America http://www.phrma.org/
- Transportation Research Board http://www.trb.org/Main/Home.aspx

Finally, we fully reviewed the references of retrieved articles in order to locate any additional relevant materials.

Search Terms Used

We searched for information on seizures using a set of specific keywords and text word combinations. All articles retrieved needed to relate to the topic of Seizure disorder, so they contained at least one keyword from column A (see table below). If results were insufficient, we switched to general driver keywords to increase search results (see column B for both search approaches). Finally, each research question had topic-specific keywords, so all articles needed to contain at least one keyword from column C. To ensure a manageable number of results, keywords needed to appear in the title/keywords/subject headers of the article rather than anywhere in the full text.

All searches were limited to the English language. For databases where large numbers of results were returned (e.g., Science Direct) search terms were further limited to header/subject/keywords. Searching was completed in October of 2018.

Keywords are presented in Table 1 below; search terms are presented in Table 1.

Table 1: Keywords

Question Number	Seizures (A)	Driving (B)	Topical (C)
1	Seizure(s), seizure disorder(s), epilepsy, convulsive disorder(s)	Driving, auto, automobile, driver, motor vehicle	Traffic accident, automobile accident, motor vehicle accident, traffic crash, automobile crash, motor vehicle crash, traffic related injury, traffic injury, automobile injury, motor vehicle injury
2	Seizure(s), seizure disorder(s),	Anti-epileptic drug(s), anti-epileptic drug treatment, anti-epileptic drug therapy, anti-	Seizure free, seizure recurrence, seizure incidence, seizure recurrence risk, seizure

	epilepsy, convulsive disorder(s)	seizure medication, anti-convulsive drug(s), anti-convulsant agent, Acetazolamide, Antiepilepsirine, Apo-acetazolamide, Apo-carbamazepine, Brivaracetam, Cannabidiol oral solution, Carbamazepine, Carbamazepine-XR, Celontin, Cerebyx, Clobazam, Clonazepam, Depakene, Depakote, Diamoz, Diazepam, Dilantin, Divalproex Sodium, Divalproex Sodium-ER, Ecovia, Epitol, Epival, Eslicarbazepine Acetate, Ethosuximide, Ezogabine, Felbamate, Felbatol, Fosphenytoin, Gabapentin, Imipramine, Keppra, Lacosamide, Lamictal, Lamotrigine, Levetiracetam XR, Lorazepam, Luminal, Mazepine, Mentat, Methsuximide, Neurontin, Novocarbamaz, Oxcarbazepine, Phenobarbital, Phenytoin, Piracetam, Pregabalin, Primidone, Remacemide, Rufinamide, Sinemet, Tegretol, Tiagabine, Tiagabine Hydrochloride, TMO, Tofranil, Topiramate, Topiramate XR, Tridione, Trileptal, Trimethadione, Trimethinum, Troxidone, Valproic acid, Vigabatrin, Zarontin, Zonegran, Zonisamide	control, follow-up, long-term, longitudinal, outcome(s)
3	Seizure(s), seizure disorder(s), epilepsy, convulsive disorder(s)	Epilepsy surgery, resective surgery, resective epilepsy surgery, laser ablation, laser therapy	Seizure free, seizure recurrence, seizure incidence, seizure recurrence risk, seizure control, follow-up, long-term, longitudinal, outcome(s)
4	Unprovoked seizure		Seizure free, seizure recurrence, seizure incidence, seizure recurrence risk, seizure

			control, follow-up, long-term, longitudinal, outcome(s)
5	Seizure(s), seizure disorder(s), epilepsy, convulsive disorder(s)	Treatment compliance, treatment adherence, medication compliance, medication adherence Serum concentration, plasma concentration, drug concentration, blood concentration, maximum concentration	Seizure free, seizure recurrence, seizure incidence, seizure recurrence risk, seizure control, follow-up, long-term, longitudinal, outcome(s)
6	Seizure(s), seizure disorder(s), epilepsy, convulsive disorder(s)	Anti-epileptic drug(s), anti-epileptic drug treatment, anti-epileptic drug therapy, anti-seizure medication, anti-convulsive drug(s)	Driving ability, driving performance, simulated driving, driver simulator, fitness to drive, driver fitness, psychomotor performance, psychomotor effects, cognitive function(ing), cognition, physiologic reaction, vision, motor function, Psychomotor Vigilance Tasks, PVT, aware(ness), choice behavior, cognition, continuous performance test, divided attention task, eye movement, reaction time, response latency, mental function, neuropsychological performance, perceptual motor processes, risk taking road tracking test

Table 2: Search Terms Used

Q1 Terms	("seizure" OR "seizures" OR "seizure disorder" OR "seizure disorders" OR "epilepsy" OR "convulsive disorder" OR "convulsive disorders") AND ("driving" OR "auto" OR "autos" OR "automobile" OR "automobiles" OR "driver" OR "drivers" OR "motor vehicle" OR "motor vehicles") AND ("traffic accident" OR "traffic accidents" OR "automobile accident" OR "automobile accidents" OR "motor vehicle accident" OR "motor vehicle accidents" OR "traffic crash" OR "traffic crashes" OR "automobile crash" OR "automobile crashes" OR "motor vehicle crash" OR "motor vehicle crashes" OR "traffic related injury" OR "traffic related injuries" OR "traffic injury" OR "traffic injuries" OR "automobile injury" OR "automobile injuries" OR "motor vehicle injury" OR "motor vehicle injuries")

Q2 Terms	("seizure" OR "seizures" OR "seizure disorder" OR "seizure disorders" OR "epilepsy" OR "convulsive disorder" OR "convulsive disorders") AND ("anti-epileptic drug" OR "anti-epileptic drugs" OR "anti-epileptic drug treatment" OR "anti-epileptic drug treatments" OR "anti-epileptic drug therapy" OR "anti-epileptic drug therapies" OR "anti-seizure medication" OR "anti-seizure medications" OR "anti-convulsive drug" OR "anti-convulsive drugs" OR "anti-convulsant agent" OR "anti-convulsant agents" OR "Acetazolamide" OR "Antiepilepsirine" OR "Apo-acetazolamide" OR "Apo-carbamazepine" OR "Brivaracetam" OR "Cannabidiol oral solution" OR "Carbamazepine" OR "Carbamazepine-XR" OR "Celontin" OR "Cerebyx" OR "Clobazam" OR "Clonazepam" OR "Depakene" OR "Depakote" OR "Diamoz" OR "Diazepam" OR "Dilantin" OR "Divalproex Sodium" OR "Divalproex Sodium-ER" OR "Ecovia" OR "Epitol" OR "Epival" OR "Eslicarbazepine Acetate" OR "Ethosuximide" OR "Ezogabine" OR "Felbamate" OR "Felbatol" OR "Fosphenytoin" OR "Gabapentin" OR "Imipramine" OR "Keppra" OR "Lacosamide" OR "Lamictal" OR "Lamotrigine" OR "Levetiracetam XR" OR "Lorazepam" OR "Luminal" OR "Mazepine" OR "Mentat" OR "Methsuximide" OR "Neurontin" OR "Novocarbamaz" OR "Oxcarbazepine" OR "Phenobarbital" OR "Phenytoin" OR "Piracetam" OR "Pregabalin" OR "Primidone" OR "Remacemide" OR "Rufinamide" OR "Sinemet" OR "Tegretol" OR "Tiagabine" OR "Tiagabine Hydrochloride" OR "TMO" OR "Tofranil" OR "Topiramate" OR "Topiramate XR" OR "Tridione" OR "Trileptal" OR "Trimethadione" OR "Trimethinum" OR "Troxidone" OR "Valproic acid" OR "Vigabatrin" OR "Zarontin" OR "Zonegran" OR "Zonisamide") AND ("seizure free" OR "seizure recurrence" OR "seizure recurrences" OR "seizure incidence" OR "seizure incidences" OR "seizure recurrence risk" OR "seizure recurrence risks" OR "seizure control" OR "seizure controls" OR "follow-up" OR "follow-ups" OR "long-term" OR "longitudinal" OR "outcome" OR "outcomes")
Q3 Terms	("seizure" OR "seizures" OR "seizure disorder" OR "seizure disorders" OR "epilepsy" OR "convulsive disorder" OR "convulsive disorders") AND ("epilepsy surgery" OR "resective surgery" OR "resective surgeries" OR "resective epilepsy surgery" OR "resective epilepsy surgeries" OR "laser ablation" OR "laser ablations" OR "laser therapy" OR "laser therapies") AND ("seizure free" OR "seizure recurrence" OR "seizure recurrences" OR "seizure incidence" OR "seizure incidences" OR "seizure recurrence risk" OR "seizure recurrence risks" OR "seizure control" OR "seizure controls" OR "follow-up" OR "follow-ups" OR "long-term" OR "longitudinal" OR "outcome" OR "outcomes")

Q4 Terms	("unprovoked seizure" OR "unprovoked seizures") AND ("seizure free" OR "seizure recurrence" OR "seizure recurrences" OR "seizure incidence" OR "seizure incidences" OR "seizure recurrence risk" OR "seizure recurrence risks" OR "seizure control" OR "seizure controls" OR "follow-up" OR "follow-ups" OR "long-term" OR "longitudinal" OR "outcome" OR "outcomes")
Q5 Terms	("seizure" OR "seizures" OR "seizure disorder" OR "seizure disorders" OR "epilepsy" OR "convulsive disorder" OR "convulsive disorders") AND ("treatment compliance" OR "treatment adherence" OR "medication compliance" OR "medication adherence") AND ("seizure free" OR "seizure recurrence" OR "seizure recurrences" OR "seizure incidence" OR "seizure incidences" OR "seizure recurrence risk" OR "seizure recurrence risks" OR "seizure control" OR "seizure controls")
Q6 Terms	("seizure" OR "seizures" OR "seizure disorder" OR "seizure disorders" OR "epilepsy" OR "convulsive disorder" OR "convulsive disorders") AND ("anti-epileptic drug" OR "anti-epileptic drugs" OR "anti-epileptic drug treatment" OR "anti-epileptic drug treatments" OR "anti-epileptic drug therapy" OR "anti-epileptic drug therapies" OR "anti-seizure medication" OR "anti-seizure medications" OR "anti-convulsive drug" OR "anti-convulsive drugs") AND ("driving ability" OR "driving abilities" OR "driving performance" OR "simulated driving" OR "driver simulator" OR "driver simulators" OR "fitness to drive" OR "driver fitness" OR "psychomotor performance" OR "psychomotor performances" OR "psychomotor effect" OR "psychomotor effects" OR "cognitive function" OR "cognitive functioning" OR "cognitive functions" OR "cognition" OR "physiologic reaction" OR "physiologic reactions" OR "vision" OR "visions" OR "motor function" OR "motor functions" OR "Psychomotor Vigilance Task" OR "Psychomotor Vigilance Tasks" OR "PVT" OR "aware" OR "awareness" OR "choice behavior" OR "choice behaviors" OR "cognition" OR "cognitions" OR "continuous performance test" OR "continuous performance tests" OR "divided attention task" OR "divided attention tasks" OR "eye movement" OR "eye movements" OR "reaction time" OR "reaction times" OR "response latency" OR "response latencies" OR "mental function" OR "mental functions" OR "neuropsychological performance" OR "neuropsychological performances" OR "perceptual motor process" OR "perceptual motor processes" OR "risk taking road tracking test")

Inclusion/Exclusion Criteria

These searches produced large numbers of search results. Our research team reviewed the title and abstract of each returned article. This information was reviewed against a set of

retrieval criteria that were defined a priori. If the article matched the criteria, it was entered into a reference database with a notation about which question it apparently applied to. Each article was obtained in full text (typically as a PDF file) and attached to the bibliographic information in the database.

The inclusion criteria were:

Retrieval Criteria for Key Question 1

- Article must be published in the English language.
- Article must be full-length and not a letter, editorial, news, comment, case report, review, note, abstract, or conference paper.
- Article must describe a study that enrolled 10 or more subjects over the age of 18.
- Article must describe a study on the risk of motor vehicle crash for individuals with recurrent seizure disorders.
- Study must be published after January 1, 2007.

Retrieval Criteria for Key Question 2

- Article must be published in the English language.
- Article must be full-length and not a letter, editorial, news, comment, case report, review, note, abstract, or conference paper.
- Article must describe a study that enrolled 10 or more subjects over the age of 18.
- Article must describe a study on the use of anti-epileptic drugs to control seizures among individuals with recurrent seizure disorder.
- Article must describe a study that shows the relationship between the use of anti-epileptic drugs and time since last seizure.
- Study must be published after January 1, 2007.

Retrieval Criteria for Key Question 3

- Article must be published in the English language.
- Article must be full-length and not a letter, editorial, news, comment, case report, review, note, abstract, or conference paper
- Article must describe a study that enrolled 10 or more subjects over the age of 18.
- Article must describe a study on use of surgical interventions for the control of recurrent seizures.
- Article must measure the success of the surgical intervention based on time since last seizure.
- Study must be published after January 1, 2007.

Retrieval Criteria for Key Question 4

- Article must be published in the English language.
- Article must be full-length and not a letter, editorial, news, comment, case report, review, note, abstract, or conference paper.
- Article must describe a study that enrolled 10 or more subjects over the age of 18.

- Article must describe a study on the likelihood of seizure recurrence among individuals who have experienced a single unprovoked seizure.
- Article must evaluate the likelihood of seizure recurrence based on time since last seizure.
- Study must be published after January 1, 2007.

Retrieval Criteria for Key Question 5

- Article must be published in the English language.
- Article must be full-length and not a letter, editorial, news, comment, case report, review, note, abstract, or conference paper.
- Article must describe a study that enrolled 10 or more subjects over the age of 18.
- Article must describe a study that examines the relationship between compliance with a prescribed regimen of anti-epileptic drug(s), as measured by drug serum levels, and treatment effectiveness, as measured by seizure cessation.
- Study must be published after January 1, 2007.

Retrieval Criteria for Key Question 6

- Article must be published in the English language.
- Article must be full-length and not a letter, editorial, news, comment, case report, review, note, abstract, or conference paper.
- Article must describe a study that enrolled 10 or more subjects over the age of 18.
- Article must describe a study that examines the effects of chronic use of anti-epileptic drugs on surrogate markers of driving safety as measured by relationship between compliance with a prescribed regimen of anti-epileptic drug(s), as measured by variables such as psychomotor performance, cognitive functioning, motor function, and psychometry vigilance.
- Study must be published after January 1, 2007.

Once all sources had been searched, the reference database was searched to eliminate duplicate articles. A researcher then reviewed each article, again against a set of exclusion and inclusion criteria. These a priori criteria, below, largely mirror the retrieval criteria, but this time the decision was made based on a review of the full-text of the article as opposed to the abstract only.

Inclusion Criteria for all Questions

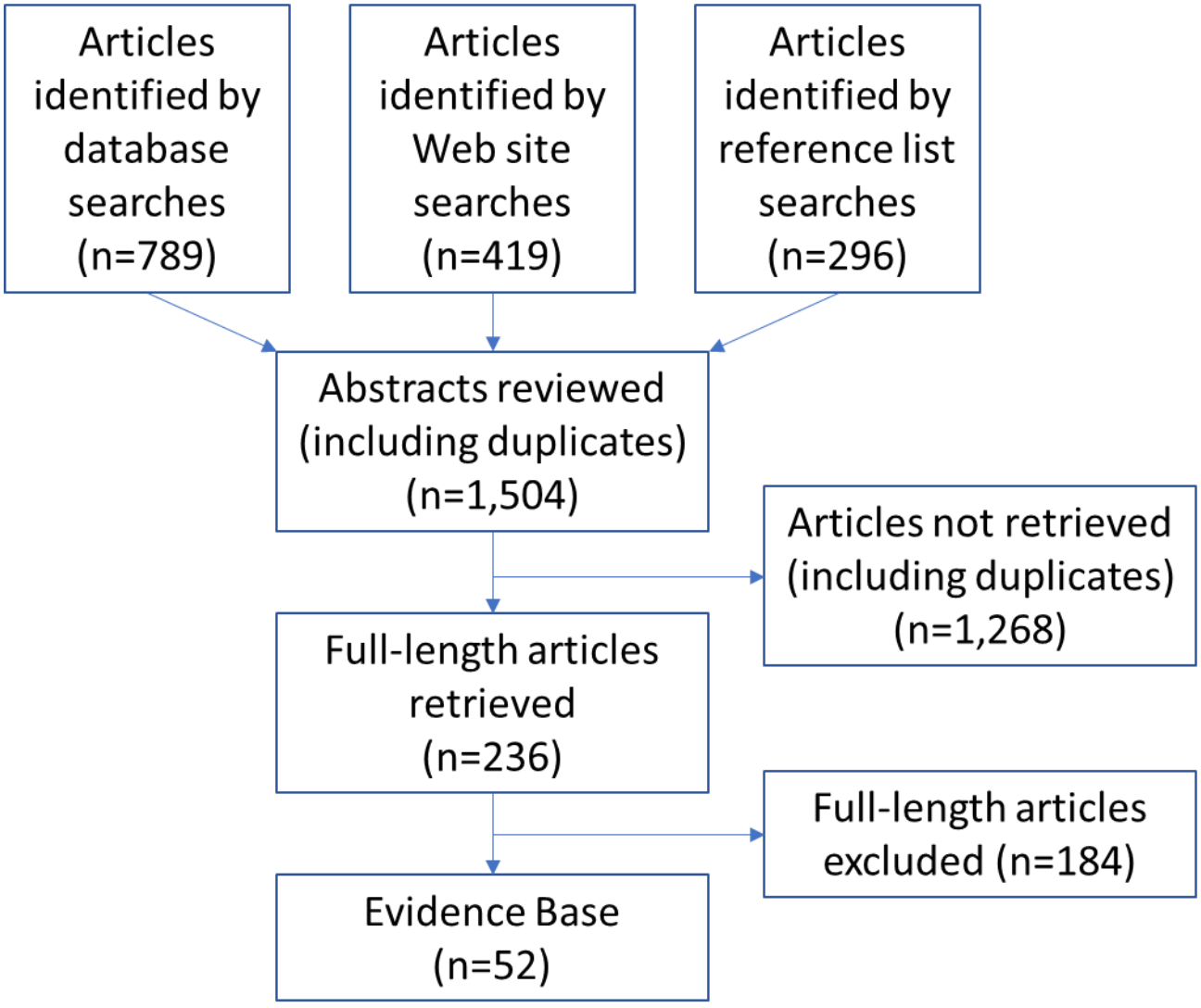
Inclusion criteria mirror the retrieval criteria, with one addition. If the same study is reported in multiple publications, the most complete publication will be the primary reference. Full-length studies were not be double counted.

Reviewers decided whether each article should be included or excluded. In cases of uncertainty, the article was flagged for follow-up and reviewed by the Principle Investigator. Reviewers were also asked to identify potentially relevant references in the identified studies.

In cases where articles were excluded, reviewers also made a notation summarizing the reason for exclusion.

Evidence Summary

A total of n=52 relevant studies were identified through our search process. These studies were identified via database searches, web site searches, and reference list searches. The search process is diagrammed below.

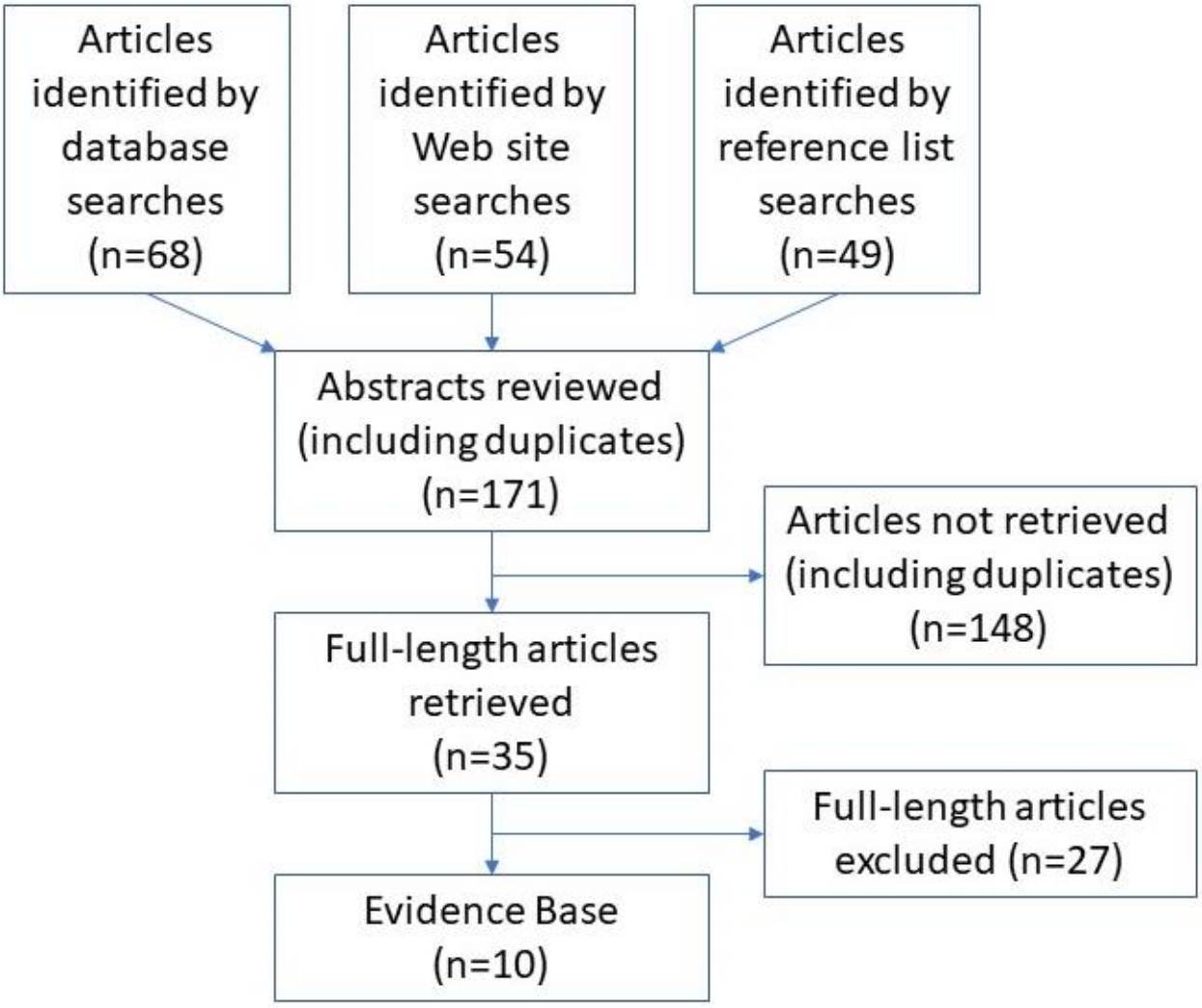


This section of the report presents findings for each research question.

Research Question 1

Evidence Base

The evidence base for Question 1 consisted of n=10 studies, as shown in the search diagram.



Summaries of Included Studies

#	Author	Year	Location of Study	Study Objective	Sample Size and Demographics	Study Design
1	Bicalho, M.A.H., L. Sukys-Claudino, R. Guarnieri, K. Lin, R. Walz	2012	Brazil	To: (1) assess the driving status of patients with epilepsy (PWE) in secondary and tertiary health centers in Florianópolis city (Southern Brazil), (2) analyze socio-demographic and clinical variables of PWE who drive, and (3) analyze the relationship between traffic accidents and these socio-demographic and clinical variables	n = 144; gender (45% female); age (> 18); age of epilepsy onset (</= 18 = 70%; > 18 = 30%); per capita income (</= 230 Reais [time period for amount not specified] = 51%; > 230 Reais = 49%)	Empirical research, including statistical records, interviews, and experimental methods
2	Bilban, M.	2008	Slovenia	Compare medical evaluations of driving capability of drivers with epilepsy with the rules of Slovenian legislation.	541 subjects: all drivers in Slovenia that were evaluated as epileptic between 1993 and 2002	Systematic review
3	Faught, E., Duh, M.S., Weiner, J.R., et al.	2008	Florida, Iowa, New Jersey	PRIMARY OBJECTIVE: investigate whether non-adherence to antiepileptic drugs (AEDs) is associated with increased mortality. SECONDARY OBJECTIVE: examine whether non-adherence to AEDs increases the risk of serious clinical events, including emergency department (ED) visits, hospitalizations, MVA injuries, fractures, and head injuries.	n = 33,658; gender (56.7% female); age (45.5% 18-39 years-old; 54.5% 40+ years-old); ethnicity (51.1% white; 21.8% African American; 19% other ethnicity; 8.2% unknown ethnicity); state/location (54.8% Florida; 8.2% Iowa; 37% New Jersey)	Retrospective open-cohort study

#	Author	Year	Location of Study	Study Objective	Sample Size and Demographics	Study Design
4	Kwon, C. Liu, M., Quan, H., et al.	2011	Canada	To compare the incidence of MVAs, attempted or completed suicides, and injuries inflicted by others between individuals with and without epilepsy	n = 51200 (10,240 with epilepsy; 40,960 without epilepsy / controls); age range = .12 - 99.4 (mean age = 39); 48.5% female	Cohort-controlled population-based study (retrospective)
5	Naik, P. A., Fleming, M. E., Bhatia, P., & Harden, C. L.	2015	Review of studies conducted in US (Arizona, Utah), Canada (Alberta, Ontario), Scandinavia (Odense, Denmark; Turku, Finland), UK	To understand the magnitude of the risk that drivers with epilepsy (DWE) contribute to motor vehicle accidents (MVA) compared to other drivers	Across 8 studies, a total sample size of 2,490,395 (30,794 DWE, and 2,459,601 controls). No specified demographics, other than drivers with epilepsy compared to general population (or, in one study, those with other medical conditions and those under the influence of alcohol)	Systematic, evidence-based review, of articles published since 1996, and available through PubMed
6	Nirkko, A.C., Bernasconi, C. von Allmen, A., Liechti, C., Mathis, J., Krestel, H.	2016	Switzerland	To investigate effects of interictal epileptic activity (IEA) and antiepileptic drugs (AEDs) on reactivity and aspects of fitness to drive for epilepsy patients	n = 46 (adults, >/= 18). At the time of the study, 78% (n = 36) of the patients had a driver's license, 22% (n = 10) did not. 65% (n = 30) were not allowed to drive, 28% (n = 13) were allowed to drive, and 7% (n = 3) had medical records that did not specify their driving fitness.	Empirical Research, including the use of direct observation, use of statistical records, and experimental methods
7	No, Y.J., Lee, S.J., Park H., Lee, S.	2011	South Korea	"To investigate the characteristics of driving in people with epilepsy and identify factors associated with driving in those with	"Of 290 epilepsy patients, 58% had a driver's license, 40% had driven during the last year. "	"Qualitative interview designed to collect each patient's socio-demographic

#	Author	Year	Location of Study	Study Objective	Sample Size and Demographics	Study Design
				uncontrolled seizures".		data and driving-related information. Clinical data related to epilepsy were collected from information in patients' medical files"
8	Pohlmann-Eden, B., Hynick, N., Legg, K.	2013	Halifax, Nova Scotia, Canada (Halifax First Seizure Clinic)	Examine data related to first seizure while driving (FSWD)	n = 13; 77% male; age range = 20 - 67; average age = 38; median age = 32	Systematic, evidence-based review
9	Saengsuwan, J., Laohasiriwong, W., Boonyaleepan,S., Sawanyawisuth, K., Tiamkao, S., Talkul, A.	2014	Thailand	To determine the number and types of falls and vehicular crashes with injuries, as well as some specific behavioral associations in people with epilepsy	n = 203; gender (52.2% male); age (range = 18 - 77; mean = 36.48); marital status (married = 55.2%; single = 39.9%; divorced or widowed = 4.9%); education (53.2% never finished high school); employment (employed = 53.3%; unemployed = 22.7%; not looking for employment because of seizures = 22.7%; changed jobs after having seizures = 23%; quit jobs entirely after having seizures = 4.4%); living situation (lived with one or more	Cross-sectional study

#	Author	Year	Location of Study	Study Objective	Sample Size and Demographics	Study Design
					relatives = 96.1%; lived alone = 3.9%)	
10	Webster, N.J., Crawford, P., Thomas, F.M.	2011	Ohio	"To examine driving in the context of people with medically intractable epilepsy, a population generally discouraged from driving".	"190 adults with medically intractable epilepsy receiving care at the Cleveland Clinic Epilepsy Center, with valid driver's license."	Retrospective and cross-sectional data were analyzed.

Quality of Included Studies

#	Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Other bias
1	Bicalho, M.A.H., L. Sukys-Claudino, R. Guarnieri, K. Lin, R. Walz	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	High Risk
2	Bilban, M.	High risk	Low risk	Low risk	Low risk	Low risk	High Risk	High Risk
3	Faught, E., Duh, M.S., Weiner, J.R., et al.	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
4	Kwon, C. Liu, M., Quan, H., et al.	High risk	Low risk:	Low risk	Low risk	High risk	Low risk	Unclear risk

#	Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Other bias
5	Naik, P. A., Fleming, M. E., Bhatia, P., & Harden, C. L.	High risk	Low Risk	Low Risk	Low risk	Low risk	Low risk	Unclear Risk
6	Nirkko, A.C., Bernasconi, C. von Allmen, A., Liechti, C., Mathis, J., Krestel, H.	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
7	No, Y.J., Lee, S.J., Park H., Lee, S.	High risk	High risk	High risk	High risk	Low risk	Low risk	Recall and self reporting bias in the interviews
8	Pohlmann-Eden, B., Hynick, N., Legg, K.	High risk	Low risk	Low risk	Low risk	High risk:	Low risk	High Risk
9	Saengsuwan, J., Laohasiriwong, W., Boonyaleepan,S., Sawanyawisuth, K., Tiamkao, S., Talkul, A.	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	High risk	Unclear risk
10	Webster, N.J., Crawford, P., Thomas, F.M.	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Recall and self reporting bias in the interviews

Findings

Ten studies addressed Research Question 1. All ten presented data on the risk of crashes experienced by individuals with epilepsy, but only two of the studies contained comparison groups of individuals who lacked the disorder. Seven of the studies [1, 3, 6, 7, 8, 9, 10] found evidence of an increased risk associated with epilepsy. Naik, et al., 2015 [5] had inconsistent findings, while Bilban, 2008 [2] and Kwon, et al., 2011 [4] found that crash risk was no higher than in the general population.

The research conducted by Nirkko [6], No [7], and Saengsuwan [9] all supported an increased risk for motor vehicle crash for people with epilepsy. Furthermore, these studies contained similar data points worthy of discussion. Nirkko found that interictal epileptic activity (IEA) increased reaction time in certain circumstances for subjects with generalized typical IEA patients by more than 26 percent, compared to the lower percentages recorded for generalized

atypical IEA subjects; subjects with generalized typical IAE had prolongations of reaction time up to 200ms. Under other circumstances, however, "if the difference in crash probability between normal EEG and IEA was analyzed according to IAE type, no statistically significant difference between focal, generalized atypical, and generalized typical IAE was found.

No [7] found that about 9 percent of people with epilepsy with a driver's license had experienced seizure-related accidents in the previous 5 years, but it was significantly higher in patients with uncontrolled seizures than in patients with controlled seizures. Moreover, 2 patients who were seizure-free reported having seizure-related accidents in the past 5 years, compared to 13 non-seizure-free patients who had accidents in the same period. This difference is statistically significant. However, the number of total accidents experienced was not statistically significantly different between the groups. Saengsuwan [9] found that 85 percent of epilepsy patients studied operate a vehicle on a regular basis, and 22 percent of those had been in an MVA. Over 40 percent of the people with epilepsy who were studied reported having either a fall or a traffic accident because of seizures. Over fifty percent of those incidents were vehicle crashes, the majority related to motorcycle use. Epilepsy patients with a low ability to control their seizures were 2.6 times more likely to have either a fall or a traffic accident than those patients who had excellent seizure control, a finding that is statistically significant. These three studies found evidence of a positive relationship, but none of these studies contained comparison groups of individuals who did not have the disorder.

However, Kwon [4] found that the incidence of MVAs among people with epilepsy was essentially the same as for people without epilepsy. Moreover, Bilban [2] found that 1.6 percent of epileptic drivers caused traffic accidents, which is lower than in the general public. This study appears to be biased towards a particular pre-conceived outcome and agenda. The results were not reported consistently, and significance testing was not conducted. These quality issues limit the validity and generalizability of the findings. Caution should be used in considering these findings as evidence against a link between seizures and motor vehicle crashes.

Kwon [4] was the only other article which found that there was not an increased risk of motor vehicle crash for people with epilepsy. This was a cohort-controlled, population-based, retrospective study, containing a much stronger methodology, findings which were reported with significance testing, analysis including Odds Ratios, and reasonable conclusions drawn from the evidence. The strength of the evidence cited in the Kwon article should be seriously considered as a possible example of seizures not being associated with motor vehicle crashes.

Some articles which found a connection also had limitations, including small sample size ([6, 8], methodological issues [7], absence of comparison groups [1, 6, 8, 9] and possible bias [3, 6,

9]. Moreover, some of the studies were retrospective and observational, and cannot determine causation, only association. Despite these limitations, the majority of the evidence reviewed here points to an affirmative relationship that people with epilepsy are more likely to be involved in an MVA.

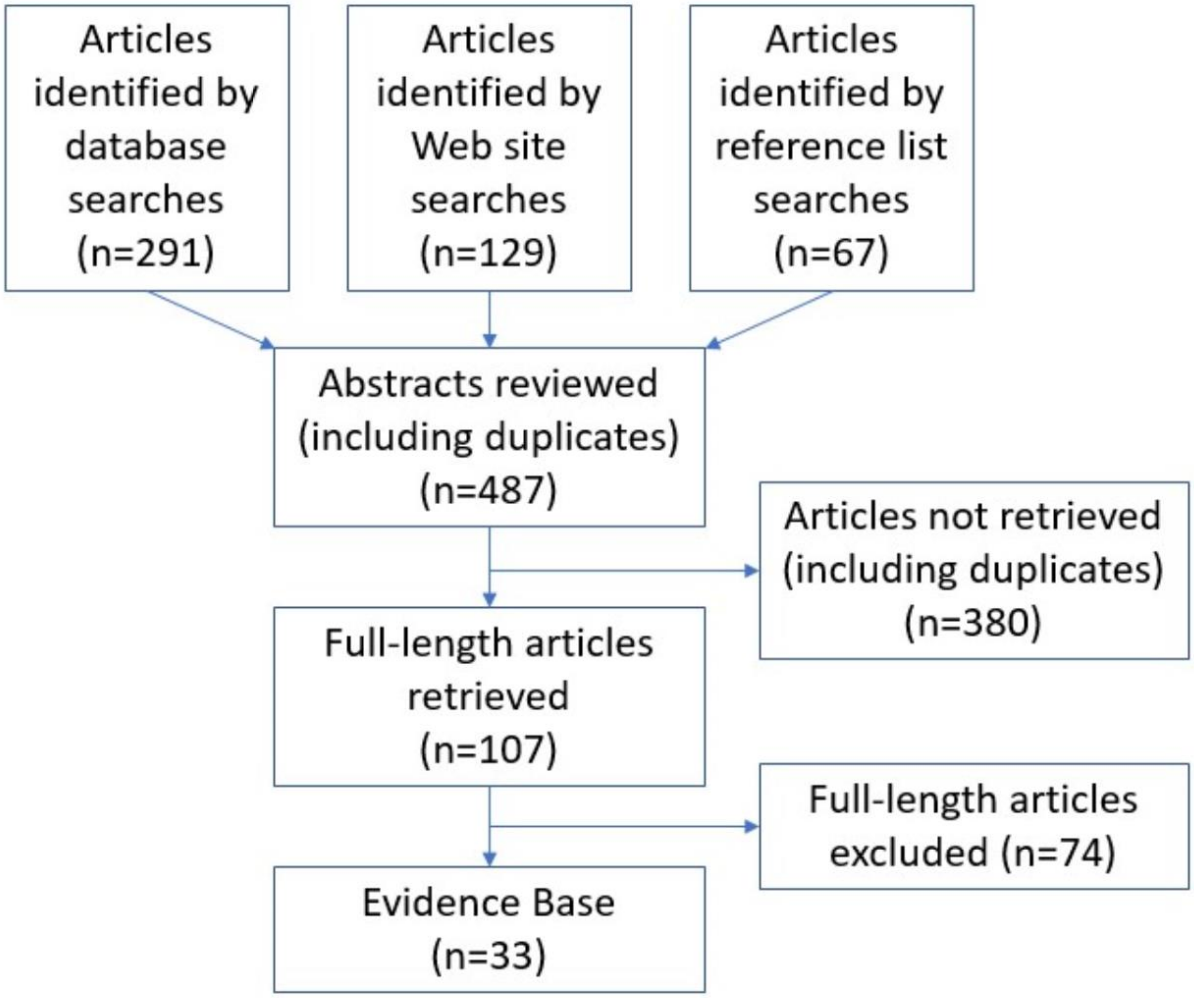
One factor which was found to increase the likelihood of being in a motor vehicle crash was age over 18 at epilepsy onset [1]. Other factors which were also associated with increased risk of accidents included non-adherence with medication prescriptions ([3, 9], lack of confidence in managing seizures [9], seizures associated with conscious impairment [1], and uncontrolled seizures ([7, 9].

There is moderate evidence to support the contention that individuals with recurrent seizure disorders (epilepsy) are at an increased risk for a motor vehicle crash as compared to comparable individuals who do not have a seizure disorder. While much of the available evidence supports this hypothesis, available studies have significant methodologic limitations and there is some contradictory evidence.

Research Question 2

Evidence Base

The evidence base for Question 2 consisted of n=33 studies, as shown in the search diagram.



Summaries of Included Studies

#	Author	Year	Location of Study	Study Objective	Sample Size and Demographics	Study Design
1	Baulac, M., Brodie, M.J., Patten, A., Segieth, J., Giorgi, L.	2012	Europe, Asia, Australia	Compare the efficacy and tolerability of once-daily zonisamide with twice-daily controlled-release carbamazepine monotherapy for such patients.	583 patients enrolled, aged 18-75. Zonisamide group completion n=281, 174 male and 107 female, mean age 37.1 (SD=16.3); carbamazepine group completion n=300, 172 male and 128 female, mean age 35.6 (SD=15.5).	Phase III, multicenter, randomized, double-blind, non-inferiority trial

2	Baulac, M., Coulbaut, S., Doty, P., McShea, C., et al.	2017	France	To evaluate the safety and effectiveness of lacosamide with the use of a flexible dose titration schedule and maintenance doses up to the maximum approved dose of 400 mg/day	100 adult focal seizure patients at 45 treatment centers across France. (74 Completed study); Age: 18 years of age or older; Diagnosed with focal seizures with or without secondary generalization; Must have presented with 1-14 seizures per 28 days over the three-month baseline period; Must have been taking 1-3 concomitant AEDs at a stable dose. Mean age=44.5 years. Age range= 19-76 years; n=45 males (45%)	Phase IV, multicentre, open-label, interventional trial conducted at 45 centers across France.

3	Baulac, M., Patten, A., Giorgi, L.	2014	France	Investigate the long-term safety and maintenance of efficacy of monotherapy with once-daily zonisamide versus twice-daily controlled-release carbamazepine for partial seizures in adults with newly-diagnosed epilepsy	Zonisamide group: n=137, median age 34.0 (18-75), 80 male and 57 female; carbamazepine group: n=157, median age 30.0 (18-75), 99 male and 59 female	Long-term, double-blind, extension study
4	Ben-Menachem, E., Biton, V., Jatuzis, D., Abou-Khalil, B., Doty, P., Rudd, G.D.	2007	Germany, Hungary, Lithuania, Poland,	Evaluate the efficacy and safety of lacosamide when added to 1 or 2 AEDs in adults with uncontrolled partial-onset seizures, and assess plasma concentrations of concomitant AEDs to determine for drug interactions.	312 subjects, 54% female, 46% male, aged between 18 and 68	Multicenter, multinational, double-blind, placebo-controlled, randomized, dose-response trial

5	Bruun, E., Kalviainen, R., Keranen, T.	2016	Finland	Assess the outcome of initial AED monotherapy in elderly patients with newly-diagnosed epilepsy and investigate probabilities of 2 or more to 5 or more years of complete seizure remission	529 patients, 253 female, 276 male; age range at onset of epilepsy was 65-94 years	Cohort study
6	Chung, S.S., Hogan, R.E., Blatt, I., Lawson P, B., Nguyen, H., Clark, A.M., Anders, B., Halvorsen, M.B.	2015	Argentina, Australia, Canada, Chile, Germany, Greece, Hungary, India, Israel, New Zealand, Poland, Russia, South Africa, Spain, United States	Evaluate long-term safety, efficacy and quality of life of 400mg or less per day of USL255, Qudexy (topiramate) extended release capsules as adjunctive therapy for partial onset seizures in adults	210; USL-USL group, n=99, mean age 38 (SD=12), 58% male; PBO-USL group, n=111, mean age 31 (SD=11), mean age 37	1-year open-label extension (OLE) study

7	Chung, S.S., Johnson, J.K., Brittain, S.T., Baroldi, P.	2016	United States, Russia, Mexico, Poland, Bulgaria, Romania, Croatia, Canada	Evaluate the long-term outcomes of adjunctive therapy with SPN-804, an extended release formulation of oxcarbazepine (OXC) in adults with refractory partial-onset seizures.	366 adults (18-65 years)	Open-label extension study of double-blind, placebo-controlled trial
8	French, J., Glue, P., Friedman, D., Almas, M., Yardi, N., Knapp, L., … Posner, H. B.	2016	New York University Comprehensive Epilepsy Center, New York, USA	To evaluate the comparative safety and adjunctive efficacy of pregabalin and gabapentin in reducing seizure frequency in patients with partial-onset seizures based on prestudy modeling showing superior efficacy for pregabalin	484 patients randomized to treatment; 359 completed study. Age: 18-80; Diagnosis of epilepsy with partial-onset seizures. Seizures must be inadequately controlled with 2-5 AEDs, and receiving 1 or 2 standard AEDs (other than pregabalin or gabapentin) with a minimum of 4 POSs (regardless of secondary generalization) during the 6-week baseline phase with no 28-day POS-free period. Gender: ~53% male; Mean age: ~35 years of age	2-arm, randomized, flexible-dose, double-blind, parallel-group, superiority study with 3 main phases: 6 weeks of baseline (screening), 9 weeks of double-blind dose escalation (titration), and 12 weeks of double-blind maintenance phase (21-week treatment phase)

9	Gil-Nagel, A., Brodie, M.J., Leroyc, R., Cyr, T.	2012	Multi-site (Texas, North Carolina, USA, and Spain)	To evaluate the long-term safety and tolerability of ezogabine/retigabine (EZG/RTG) in adults with partial-onset seizures; to determine the long-term efficacy of EZG/RTG	"N=336 Partial Onset Seizure patients who completed previous studies; mean (SD) age was 36.6 (11.87) years; three (<1%) patients were aged ≥65 years"	Observational safety and efficacy study of long-term, open-label extensions (OLEs)
10	Giráldez, B.G., Toledano, R., Garcia-Morales, I., Gil-Nagel, A., Lopez-Gonzalez, F.J., Tortosa, D., Ojeda, J., Serratosa, J.M.	2015	Spain	Report the efficacy and tolerability of lacosamide (LCM) monotherapy as a first-line and conversion regimens in the treatment of patients with partial-onset seizures	Group 1: n=18 (11 female, 7 male), mean age 53.1 (range=18-90). Group 2 is excluded.	Open-label extension study of a randomized, double-blind placebo-controlled trial
11	Halasz, P., Cramer, J.A., Hodoba, D., et al.	2010	Europe (Various countries)	Evaluate the long-term efficacy and safety of once-daily eslicarbazepine acetate (ESL) as adjunctive therapy for partial-onset seizures in adults with epilepsy.	239 patients, mean age 38.6 (SD=11.9), ranged from 18-76 years; 52.2% male and 47.8% female.	One-year open-label treatment extension of a placebo-controlled pivotal study

12	Hamer, H., Baulac, M., McMurray, R., Kockelmann, E., H., H., M., B., … E., K.	2016	Germany, Norway, Denmark, Sweden	To gather real-life data on retention and modalities of zonisamide use when administered as only add-on treatment to a current AED monotherapy in adult patients with partial-onset seizures.	100 adult partial-onset seizure patients in 4 countries; 93 could be evaluated. Diagnosed with Epilepsy with POS, insufficiently controlled by current monotherapy, requiring additional zonisamide (ZNS) to the regimen. Gender: 46% male; Median age was 46 years (Range: 19–87); 26% of the patients were older than 60 years. Mean time since diagnosis 13.4 years.	Multi-center observational study was performed in 4 European countries
13	Hufnagel, A., Ben-Menachem, E., Gabbai, A.A., Falcao, A., Almeida, L., Soares-da-Silva, P.	2012	Argentina, Australia, Belgium, Brazil, Denmark, Germany, The Netherlands, Portugal, Romania, South Africa, Spain, Sweden, UK	Evaluate the long-term safety, tolerability and efficacy of once-daily eslicarbazepine acetate (ESL) as an adjunctive therapy in adults with partial-onset seizures	n=325; age ranged from 18 to 69, 52.3% male and 47.7% female; mean seizure frequency of any type was 13.8 (SD=14.0) per 4 weeks (range=2.0-88.4)	Open-label extension study of a randomized, double-blind placebo-controlled trial

14	Lancman, M.E., Fertig, E.J., Tobliger, R.W., Perrine, K., Muyers, L., Iyengar, S.S., Malik, M.	2016	United States	Examine the cognitive and quality-of-life measures and outcomes with adjunctive lacosamide therapy in patients with treatment-resistant partial epilepsy?	34 patients (13 male, 21 female); mean age = 38.8 (SD=2.43 years)	Prospective, open-label, non-blinded, adjunctive therapy test-retest (within subjects)
15	Lossius, M.I., Hessen, E., Mowinckel, P., Stavem, K., Erikssen, J., Gulbrandsen, P., Gjerstad, L.	2008	Norway	To assess the effects of AED withdrawal on cognitive functions, seizure relapse, health-related quality of life (HRQOL), and EEG results	Patients selected from epilepsy registries of a hospital and six neurological outpatient clinics in Oslo, Norway. Inclusion was stopped when 168 had given their informed consent to participate. 241 patients assessed for eligibility, were reduced to 160 who were finally included for randomization (79 to withdrawal and 81 to continued medication).	Controlled, prospective, randomized, double-blinded withdrawal study

16	Lu, Y., Yu, W., Wang, X.	2009	China	Evaluate the efficacy of topiramate in the treatment of adult patients with symptomatic epilepsy of varying etiologies.	227 patients (110 male, 117 female); mean age 28.0 (SD 9.4), range 18-65	Open-label, long-term, retrospective observation
17	Maschio, M., Dinapoli, L., Mingoia, M., Sperati, F., Pace, A., Pompili, A., Carapella, C.M., Vidiri, A., Muti, P.	2011	Italy	Evaluate the efficacy and tolerability of lacosamide as an add-on in brain tumor related epilepsy	14 patients, aged 22-63, 8 male and 6 female	Case series
18	Maschio, M., Dinapoli, L., Zarabla, A., Pompili, A., Carapella, C.M., Pace, A., Giannerelli, D., Occhipinti, E., Jandolo, B.	2008	Italy	Investigate the efficacy and tolerability of topiramate (TPM) in brain tumor associated epilepsy.	47 adult patients, 24 male and 23 female, mean age, 47.6 (SD=12.6); types of seizures were as follows: 19 simple partial, 4 complex partial, 24 partial with secondary generalization	Prospective observational study

19	Maschio, M., Zarabla, A., Maialetti, A., Fabi, A., Vidiri, A., Villani, V., Giannarelli, D.	2017	Italy	Evaluate the effect of lacosamide (LCM) as an add-on therapy on seizure control and quality of life in patients with brain tumor related epilepsy.	25 adult patients, 18 male and 7 female, mean age 41.9	Prospective observational study with historical control group
20	Panagariya, A., Surekha, R.K., Sharma, B., Hrishikesh, K., Agarwal, N.	2011	North-west India	To determine clinical profile of epilepsy in response to drug therapy; To study effects of reduced dosages of anti-epileptic drugs after seizure-free intervals of 2 years	904 epilepsy patients attending OPD clinic in the department of Neurology, SMS Medical College and Hospital in Jaipur, India from 2001-2006	Observational

21	Pierre-Louis, S., Brannegana, R. T., Evans, A.T.	2009	Chicago, Illinois, USA	To assess changes in seizure frequency, medication side effects (especially tremor) and formulation after switching patients IR to ER divalproex sodium. To address study limitations by evaluating more patients over a longer period, and more comprehensively assessing most common AEDs	N=47 patients. Most were African American or Hispanic; Mean age was 35 years (range, 19–65 years); nearly 60% had partial seizures with secondary generalization. Epilepsy mostly caused by Traumatic brain injury and idiopathic epilepsy; Etiology unknown for a quarter of subjects.	Open-label prospective cohort study of adult outpatients with epilepsy; patients were taking standard divalproex for at least the preceding 6 months prior to enrollment.
22	Remi, C., Lorenzl, S., Vyhnalek, B., Rastorfer, K., Feddersen, B.	2014	Germany	Evaluate the tolerability and clinical effects of subcutaneous levetiracetam for the treatment of epileptic seizures in a palliative care setting	20 patients (11 male, 9 female), median age 69 (range 42-82)	Retrospective chart review

23	Rosenfeld, W., Fountain, N.B., Kaubrys, G., Ben-Menachem, E., McShea, C.	2014	Germany, Hungary, Lithuania, Poland, Sweden, Switzerland, the United Kingdom, and the United States	To evaluate long-term (up to 8 years of exposure) safety and efficacy of lacosamide	"n=370 patients. Mean age was 40.8 ± 11.0 years, 52% were female. Mean time since diagnosis was 25.3 ± 12.6 years. More than half (52%) had tried ≥7 lifetime AEDs and most (82%) were taking 2 concomitant AEDs at the baseline of their respective previous trial."	Prospective, multicenter, multinational, phase II OLE trial in patients with POS who were previously enrolled in one of two open-label trials, or a double-blind placebo-controlled trial of lacosamide.
24	Rossetti, A.O., Jeckelmann, S., Novy, J., Roth, P., Weller, M., Stupp, R.	2014	Switzerland	Determine the safety and efficacy of AED monotherapy with levetiracetam (LEV) or pregabalin (PBG) in patients with primary brain tumors and epilepsy and to collect prospective data on seizure control in brain tumor patients	LEV group: n=25 (9 female, 16 male) mean age=54.5 (SD=12.7). PGB group: n=27 (12 female, 15 male) mean age=52.7 (SD=10.9)	Pragmatic open label phase II randomized trial

25	Ryvlin, P., Kalviainen, R., Von Raison, F., Giordano, S., Emir, B., Chatamra, K.	2009	Belgium, Finland, France, the Netherlands, Poland, Portugal, Switzerland, UK	Evaluate the efficacy of pregabalin as adjunctive treatment in patients with refractory seizures	476 patients, 51% men and 49% women, mean age 40.1 (SD= 12.6)	Open-label study
26	Stefan, H., Hubbertz, L., Peglau, I., et al.	2008	Germany	Explore effectiveness, tolerability, and quality of life in elderly patients with epilepsy treated with topiramate.	107 patients (53% male) mean age = 69 years	Open-label, flexible-dosing clinical trial
27	Steinhoff, B.J., Bacher, M., Bucurenciu, I., Hillenbrand, B., Intravooth, T., Kornmeier. R., et al.	2017	Germany	To assess the efficiency of brivaracetam in a tertiary referral epilepsy center	101 patients (mean age 42 years, range 18–81 years, 54 females,) w	Prospective treatment study
28	Szaflarski, J.P., Lindsell, C.J., Zakaria, T., Banks, C., Privitera, M.	2010	Cincinnati, OH USA	To determine the clinical and EEG factors associated with medication response in these idiopathic generalized epilepsy (IGE) patients	322 patients with IGEs were identified in the outpatient clinic of the Cincinnati Epilepsy Center between November 2008 and 2009.	Retrospective, observational study

29	Valentin, A., Moran, N., Hadden, R., Oakes, A., Elwes, R., Delamont, R., Mullatti, N., Nashef, L.	2008	United Kingdom	Identify the clinical usefulness and side effects of add-on pregabalin (PGB) in out-patient epilepsy clinics	96 patients, 44 male and 52 female, age ranging from 21-84 years (mean 43.5).	Audit
30	Villanueva, P., Bermejo, J., Montoya, M., et al.	2016	Spain	To evaluate real- life experience (effectiveness and tolerability) with eslicarbazepine acetate (ESL) after first monotherapy failure in a large series of patients with focal epilepsy	253 patients were included in the study. ESL was required in 157 patients (62.3%) because of in-adequate efficacy of their baseline AED monotherapy, Safety population comprised all 253 patients. Efficacy population comprised 252 patients. 21 patients had no seizures 1-year prior to starting ESL.	Multi-center, retrospective, 1-year, observational, open-label, non-interventional audit of clinical records, conducted at 16 hospitals in Spain

31	Villanueva, V., López, F.J., Serratosa, J.M., et al.	2013	Spain (Multi-center study)	To examine the efficacy and tolerability of add-on lacosamide for treatment of epilepsy.	500 adult patients with focal epilepsies in Spain; 46% female. Mean age = 42 with a range of 18-88	Multicenter, retrospective, observational study (LACO-EXP) in 13 tertiary hospital centers in Spain; Study involved 500 adult patients with focal epilepsies examined the efficacy and tolerability of add-on lacosamide
32	Werhahn, K.J., Trinka, E., Dobesberger, J., et al.	2015	Germany, Austria, Switzerland	Compare the effectiveness of controlled-release carbamazepine (CR-CBZ) to levetiracetam (LEV) and to lamotrigine (LTG) in elderly patients with newly-diagnosed focal epilepsy.	359 patients, CR-CBZ group, n=121; LTG group, n=117; LEV group: n=122. Mean age 71.4 years, ranged from 60-95.	Randomized, double-blind, active comparison, multicenter, parallel-group trial
33	Zahnert, F., Krause, K., Immisch, I., Habermehl, L., Gorny, I., Chmielewska, I., et al.	2018	Germany	To assess first clinical experiences with brivaracetam (BRV) in the treatment of epilepsies	N= 93 patients at Baseline. Mean age=44 years. 62% male; 38% female	Retrospective record review from electronic patient records. Data on safety and efficacy were evaluated retrospectively.

Quality of Included Studies

#	Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Other bias
1	Baulac, M., Brodie, M.J., Patten, A., Segieth, J., Giorgi, L.	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
2	Baulac, M, Coulbaut, S., Doty,P., McShea, C., et al.	High risk:	High risk	High risk:	High risk	Unclear risk:	Low risk	Low risk
3	Baulac, M., Patten, A., Giorgi, L.	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
4	Ben-Menachem, E., Biton, V., Jatuzis, D, Abou-Khalil, B., Doty, P., Rudd, G.D.	Low Risk	Low risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
5	Bruun, E., Kalviainen, R., Keranen, T.	High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
6	Chung, S.S., Hogan, R.E., Blatt, I., Lawson P, B., Nguyen, H., Clark, A.M., Anders, B., Halvorsen, M.B.	High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
7	Chung, S.S., Johnson, J.K., Brittain, S.T., Baroldi, P.	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk
8	French, J., Glue, P., Friedman, D., Almas, M., Yardi, N., Knapp, L., … Posner, H. B.	Low risk: Randomize	Unclear risk	Low risk	High risk	Low risk:	Low risk	Unclear risk:
9	Gil-Nagel, A., Brodie, M.J ., Leroyc, R., Cyr, T.	High risk	High risk	Unclear risk	High risk	Low risk	Low risk:	Low risk
10	Giráldez, B.G., Toledano, R., Garcia-Morales, I., Gil-Nagel, A., Lopez-Gonzalez, F.J., Tortosa, D., Ojeda, J., Serratosa, J.M.	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

11	Halasz, P., Cramer, J.A., Hodoba, D., et al.	High Risk	High Risk	High Risk	High Risk	Low risk	Low risk	Low risk
12	Hamer, H., Baulac, M., McMurray, R., Kockelmann, E., H., H., M., B., … E., K.	High risk	High risk	High risk	High risk	Low risk	Low risk	Unclear risk
13	Hufnagel, A., Ben-Menachem, E., Gabbai, A.A., Falcao, A., Almeida, L., Soares-da-Silva, P.	High Risk	High Risk	High Risk	High Risk	Low risk	Low risk:	Low risk
14	Lancman, M.E., Fertig, E.J., Tobliger, R.W., Perrine, K., Muyers, L., Iyengar, S.S., Malik, M.	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk
15	Lossius, M. I., Hessen, E., Mowinckel, P., Stavem, K., Erikssen, J., Gulbrandsen, P., Gjerstad, L.	Low risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
16	Lu, Y., Yu, W., Wang, X.	High Risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
17	Maschio, M., Dinapoli, L., Mingoia, M., Sperati, F., Pace, A., Pompili, A., Carapella, C.M., Vidiri, A., Muti, P.	High Risk	High Risk	High Risk	High risk	Low Risk	Low risk	Low Risk
18	Maschio, M., Dinapoli, L., Zarabla, A., Pompili, A., Carapella, C.M., Pace, A., Giannerelli, D., Occhipinti, E., Jandolo, B.	High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
19	Maschio, M., Zarabla, A., Maialetti, A., Fabi, A., Vidiri, A., Villani, V., Giannarelli, D.	High risk	High risk	High risk	High risk	Low risk	Low risk:	Low risk

20	Panagariya, A., Surekha, R.K., Sharma, B., Hrishikesh, K., Agarwal, N.	High risk:	High risk:	High risk	High risk	Low risk	Low risk	Unclear risk
21	Pierre-Louisa, S., Brannegana, R.T., Evans, A.T.,	High risk	High risk	High risk	Low risk -	Low risk	Unclear risk	Low risk
22	Remi, C., Lorenzl, S., Vyhnalek, B., Rastorfer, K., Feddersen, B.	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk
23	Rosenfeld, W., Fountain, N.B., Kaubrys, G., et al.	High risk	High risk	Unclear risk	High risk	Low risk	Low risk:	Low risk
24	Rossetti, A.O., Jeckelmann, S., Novy, J., Roth, P., Weller, M., Stupp, R.	Low risk	High risk	High risk	High risk	Low risk	Low risk:	Low risk
25	Ryvlin, P., Kalviainen, R., Von Raison, F., Giordano, S., Emir, B., Chatamra, K.	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk
26	Stefan, H., Hubbertz, L., Peglau, I., Berrouschot, J., Kasper, B., Schreiner, A., Krimmer, J., Schauble, B.	High risk:	High risk:	High risk	High risk	Low risk	Low risk	Unclear Risk
27	Steinhoff, B.J., Bacher, M., Bucurenciu, I., Hillenbrand, B., Intravooth, T., Kornmeier. R., et al.	High Risk	Low risk	Low risk	Low risk	Low risk	Low risk	High Risk
28	Szaflarski, J.P., Lindsell, C.J., Zakaria, T., Banks, C., Privitera, M.	High risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
29	Valentin, A., Moran, N., Hadden, R., Oakes, A., Elwes, R., Delamont, R., Mullatti, N., Nashef, L.	High Risk	High Risk	High Risk	High risk	Low Risk	Low Risk	Low Risk

30	Villanueva, P., Bermejo, J., Montoya, M., et al.	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
31	Villanueva, V., López , F.J., Serratosa, J.M., et al.	High risk	Unclear Risk	Low risk	Low risk	Low risk	Low risk:	Unclear Risk
32	Werhahn, K.J., Trinka, E., Dobesberger, J., Utenberger, I., Baum, P., Deckert-Schmitz, M., Kniess, T., Schmitz, B., Bernedo, V., Ruckes, C., Ehrlich, A., Kramer, G.	Low risk	Low Risk	Low risk	Low Risk	Low Risk	Low Risk	Low Risk
33	Zahnert, F., Krause, K., Immisch, I., Habermehl, L., Gorny, I., Chmielewska, I., et al.	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk

Findings

The purpose of this section of the evidence report was to describe a relationship between the likelihood of seizures reoccurring in the following year among individuals with epilepsy who have been successfully treated and have remained seizure free with AEDs.

Thirty-three of the studies that were initially identified met all our inclusion criteria for this key question. Approximately 80 percent of these studies found an inverse relationship between the likelihood of recurrence of a seizure and the TSLS among individuals who were receiving AED treatment. Twenty seven of these 34 articles reported that, with various AED treatments, the likelihood of seizure recurrence is reduced and TSLS is increased. However, few of these studies included control groups and the results generally describe association rather than causation. In addition, many of the articles described treatment with different specific drugs, and consequently the summary below is organized by drug treatment.

Lacosamide (8 studies)

Eight studies found that treatment with lacosamide (Vimpat) reduced the likelihood of seizure recurrence and increased the TSLS [2, 4, 10, 14, 19, 23, 31, 33]. Baulac et al., 2017 [2] found flexible dosing schedules for lacosamide to be safe, tolerable, and effective in controlling seizures. Villanuevaa et al., 2013 [31] found that the efficacy was improved when

lacosamide was the first or second add-on AED, and that slower increase in dosage was associated with a lower adverse event rate. With a response rate of 86 percent, Maschio et al., 2017 [19] found lacosamide to be more effective than levetiracetam as an add-on treatment.

In a long-term follow-up study in 8 countries over 8 years, of 370 patients, Rosenfeld et al., 2014 [23] reported reduced seizure frequencies of 47–65 percent, and those for ≥50 percent response rates ranged from 49–63 percent for 1-, 3-, and 5-year completer cohorts. It was concluded that lacosamide is well-tolerated and effective and its safety is similar to the results of previous studies for up to eight years. Ben-Menachem et al., 2007 [4] achieved responder rates 11 to 19 percent greater in the lacosamide treatment groups, when compared to a placebo (22 percent). When used as an adjunct drug, lacosamide significantly reduces the frequency of seizures in patients with uncontrolled partial-onset seizures. Lancman et al., 2016 [14] found that when used as an adjunctive therapy for the treatment of resistant partial epilepsy, lacosamide poses low risks of significant changes in cognition or quality of life. This body of evidence found lacosamide to be a safe and effective drug for adjunct and monotherapy treatment of various seizure disorders, e.g. for reducing recurrence and increasing the TSLS.

Topiramate (n=4)

Four studies concluded that treatment with topiramate (Topamax) reduces the likelihood of seizure recurrence, and increases the TSLS [7, 16, 18, 26]. Lu et al., 2009 [16] found that topiramate was effective and well-tolerated as both monotherapy and an adjunct therapy for epilepsy. Chung et al., 2016 [7] found topiramate to be safe and effective in treating refractory partial onset seizures, with a median reduction in weekly partial onset seizure frequency of 56 percent. Stefan et al., 2008 [26] achieved at least a 50 percent reduction in seizure frequency among 78 percent of patients who had seizures at the beginning of the study, and 44 percent of patients were seizure-free throughout the trial. Elderly patients reported reductions in seizures, good tolerance and significant improvement in several aspects of the quality of life. Maschio et al., 2008 [18] also found tolerance and efficacy in controlling seizures in patients with epilepsy associated with brain tumors when treated with topiramate.

Eslicarbazepine acetate (ESL) (n=3)

Three studies found eslicarbazepine acetate (Aptiom, ESL) to be safe and effective in reducing likelihood of recurrence of seizures, and increasing the TSLS [11, 13, 30] Villanueva [30] found that when used after a first monotherapy failure, ESL was associated with good seizure control and tolerance. Halasz [11]and Hufnagel [13] both found that ESL provides a sustained therapeutic effect, and achieves favorable tolerance and safety.

Zonasamide (n=2)

Baulac et al., 2014 [3] and Hamer et al., 2016 [12] both concluded that treatment with zonasamide (Zonegran) is safe and effective in reducing the likelihood of seizure recurrence and increasing the TSLS. When using zonasamide as a monotherapy, administered once-daily, Baulac demonstrated long-term safety and efficacy in treatment of partial seizures in newly-diagnosed epilepsy patients, and Hamer used it successfully as an add-on therapy. This latter study achieved reduction of seizure frequency of at least 50 percent in 80 percent of the patients, with 44 percent of patients reporting freedom from seizures over three months. From these two articles, it seems that zonasamide is effective both as a monotherapy and an adjunct therapy for the treatment of epilepsy.

Pregabalin (PGB) (n=2)

Ryvlin et al., 2009 [25] and Valentin et al., 2008 [29] both concluded that pregabalin (Lyrica) could be used safely and effectively as an adjunct therapy for treating refractory seizures. Ryvlin found a 33 percent median reduction in the frequency of seizures, while 39 percent of patients experienced a reduction in frequency of ≥50 percent. Some 19 percent and eight percent of patients were seizure-free during the last 4 weeks or 12 weeks of treatment, respectively. Efficacy was consistent with that observed in previous studies, but no control group was used.

Five articles were found describing effective seizure treatment studies with other drugs, including oxcarbazepine (OXC) (Chung et al., 2016 [7]), levetiracetam (LEV) (Remi et al., 2014 [22] and Rossetti et al., 2014 [24]), ezogabine (Retigabine) (Gil-Nagel et al., 2012 [9]), and brivaracetam (BRV) (Zahnert et al., 2018 [33]). Rossetti found that both levetiracetam and pregabalin were effective treatments for seizures and Remi found that levetiracetam could also be administered subcutaneously to treat seizures. Chung found that oxcarbazepine was an effective once-daily adjunct therapy for refractory partial-onset seizures, while Gil-Nagel found ezogabine (Retigabine) to be safe and effective for long-term maintenance treatment of recurring seizures. Zahnert determined that brivaracetam was a safe, easy, and effective option for treating patients with epilepsy, especially those with psychiatric comorbidities who might not be suitable candidates for levetiracetam.

AED Monotherapy in general (n=2)

Panagariya et al., 2011 [20] and Bruun et al., 2016 [5] described the use of anti-epileptic drugs (AEDs) as a monotherapy for treatment of seizures and epilepsy, respectively. Most of the patients in the first study (Panagariya) experienced seizure control through monotherapy, most commonly with valproate, followed by phenytoin and carbamazepine. The average daily maintenance dose could be safely reduced after two seizure-free years, and Bruun found that the expectation of seizures in elderly patients with newly-diagnosed epilepsy was good, with most patients being treated successfully with the first AED that they used. Patients who

did not become seizure-free within the first year were found to be at risk of a drug-resistant seizure disorder.

Seven other articles found [1, 8, 15, 21, 27, 28, 32] also reported the efficacy of AED treatment in reducing the likelihood of seizure recurrence. One such study by Lossius et al., 2008 [15] investigated withdrawal of AED treatment which increased the likelihood of seizure relapse by 2.46 times. However, most of these 7 studies did not specifically investigate this recurrence in relation to time since last seizure.

Five of these seven studies compared two or more AED treatments, but did not detect any differences in seizure frequency between treatments [1, 8, 21, 27, 32]. The study by French et al., 2016 [8] found no significant difference between pregabalin and gabapentin in a 28-day seizure rate. Pierre-Loius et al., 2009 [21] found no difference in seizure frequency between two formulations of a single AED (immediate-release and extended-release divalproex sodium acid). When comparing controlled-release carbamazepine to levetiracetam or lamotrigine, Werhahn et al., 2015 [32]found no significant differences in rates of seizure freedom or time to first seizure. Baulac [1] found that zonisamide was non-inferior, but not superior, to controlled-release carbamazepine in terms of the proportion of patients remaining seizure free at 26 weeks. In a study by Steinhoff et al., 2017 [27], the authors found a similar rate of seizure freedom with brivaracetam, compared to lacosamide.

Seizure recurrence rate was shown to correspond to several factors, including increased risk with focal EEG abnormalities (Szaflarski et al., 2010 [28]), and decreased risk with a normal neurological examination (Lossius [15]), presence of *petit mal* seizures (Szaflarski [28]), the use of carbamazepine prior to AED withdrawal (Lossius), and high initial response to valproate treatment (Szaflarski).

Some of these articles had limitations, including small sample size [10, 14, 17, 18, 19, 21, 22, 24], methodology issues [8, 21, 27, 28, 33], lack of comparison groups [25], and possible bias [27, 28]. In one study (French [8]), the results could not be generalized to other epilepsy populations because of atypical response rates in the study. Moreover, some of the studies were retrospective and observational, and cannot determine causation, but only association.

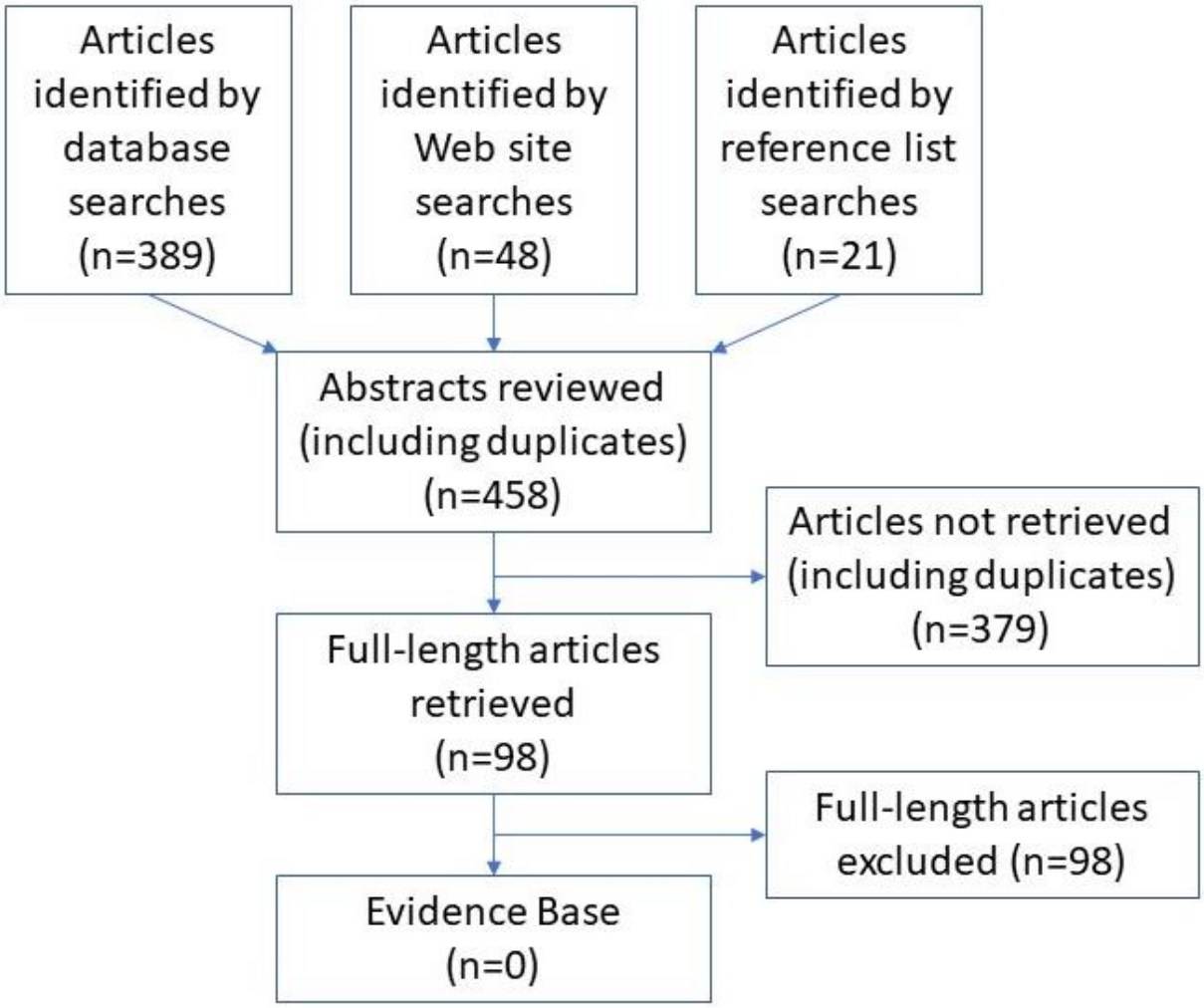
Six articles however described their use of placebo-control groups for comparison of treatment effects [4, 7, 11, 13, 15, 23]. Five other studies [1, 3, 4, 15, 32] are examples of stronger, higher-quality studies with lower risks of bias. These studies were characterized by elements, such as placebo control comparison groups, randomization and blinding of participants, large sample sizes, and prospective and longer-term studies.

Despite the aforementioned limitations, the preponderance of evidence reviewed here from individuals treated with AEDs supports an inverse relationship between the likelihood of seizure recurrence and the TSLS. As a result of these studies, it is difficult to compare effectiveness of AED treatment across drugs. It seems many of the drugs are somewhat effective in treating seizures, and that the differences in response may lie in factors including the type and severity seizure disorder. **There is moderate evidence supporting the association between AED treatment and the reduced likelihood of seizure recurrence and increased TSLS.**

Research Question 3

Evidence Base

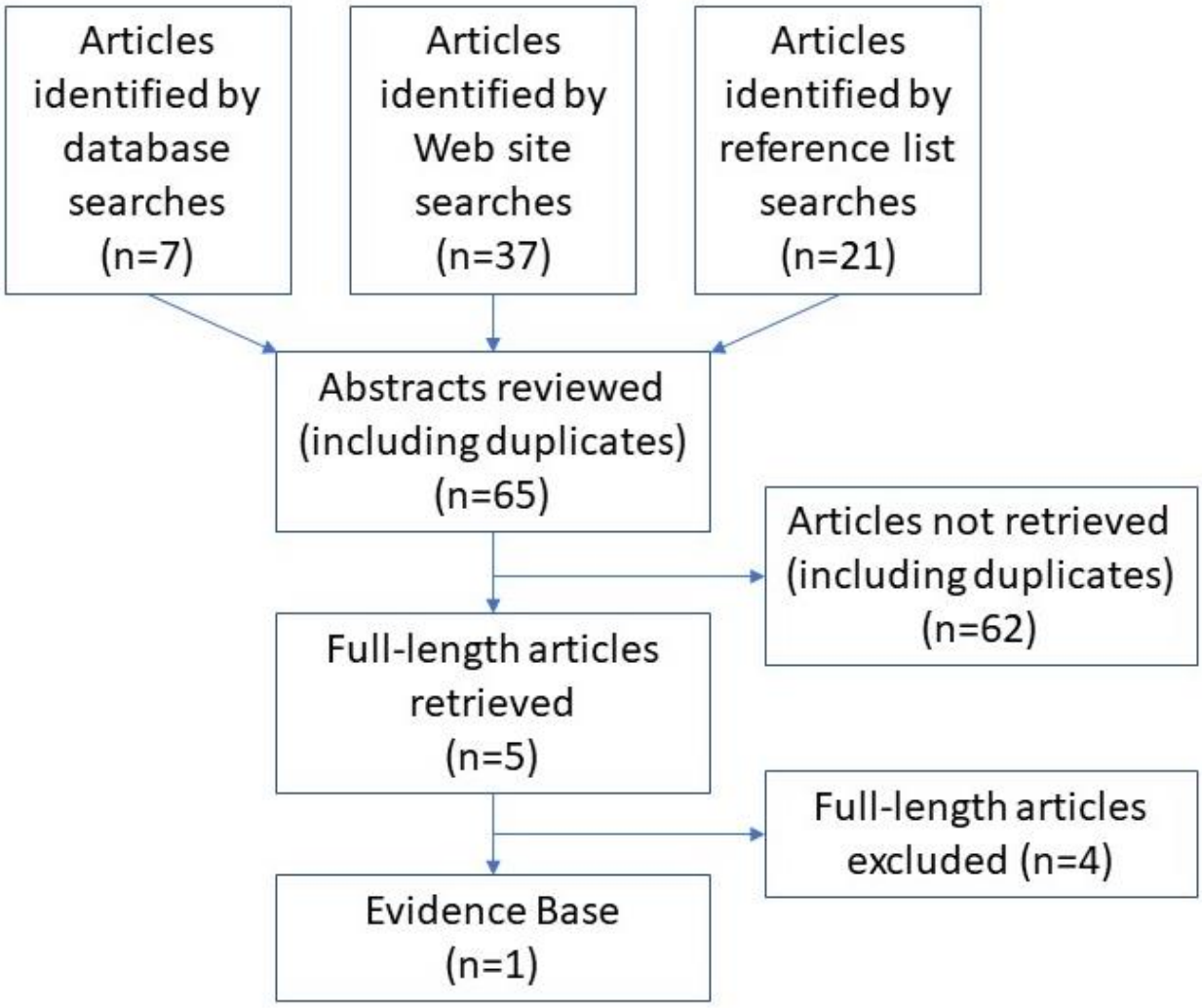
The evidence base for Question 3 consisted of n=0 studies, as shown in the search diagram.



Research Question 4

Evidence Base

The evidence base for Question 4 consisted of n=1 study, as shown in the search diagram.



Summaries of Included Studies

#	Author	Year	Location of Study	Study Objective	Sample Size and Demographics	Study Design
1	Najafi, M. R., Mehrabi, A., Najafi, F., M.R., N., A., M., & F., N.	2008	Iran	Investigate likelihood of second attack and seizure-free survival time with and without early treatment	71 males and 66 females. Adult patients with first idiopathic generalized seizures; 150 patients of single unprovoked generalized seizure.	Case-control study

Quality of Included Studies

#	Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Other bias
1	Najafi, M. R., Mehrabi, A., Najafi, F., M.R., N., A., M., & F., N.	Unclear risk	Unclear risk	High risk	High risk	Low risk	Low risk	Low risk

Findings

A paucity of research articles reporting the likelihood of seizure recurrence among individuals who have experienced a single, unprovoked seizure precludes a summary conclusion of evidence. Findings from a single qualifying study are presented here.

A keyword search of six research databases yielded seven articles. A review of these citations identified five possible articles to include. Upon further review, three articles were disqualified due to study subject characteristics, and one article because it lacked information

regarding time since last seizure. One article was found to have sufficient characteristics for inclusion in the Research Question 4 review.

This single qualifying study (Najafi et al., 2008) found a 3.8-month mean of no relapse since last seizure for 20 percent of the patients who did not receive treatment (Control group). In contrast, a 6-month mean of no relapse since last seizure was found for 49 percent of the patients in the carbamazepine treatment group.

Significant decreases in the relapse rate and prolonged seizure-free survival time occurred after the first seizure in patients exposed to early treatment. Despite treatment, some patients still relapsed; therefore, treatment with carbamazepine could not guarantee seizure freedom.

Thus, this article found that the relationship between seizure recurrence and time since last seizure could be increased by 2.2 months with carbamazepine treatment.

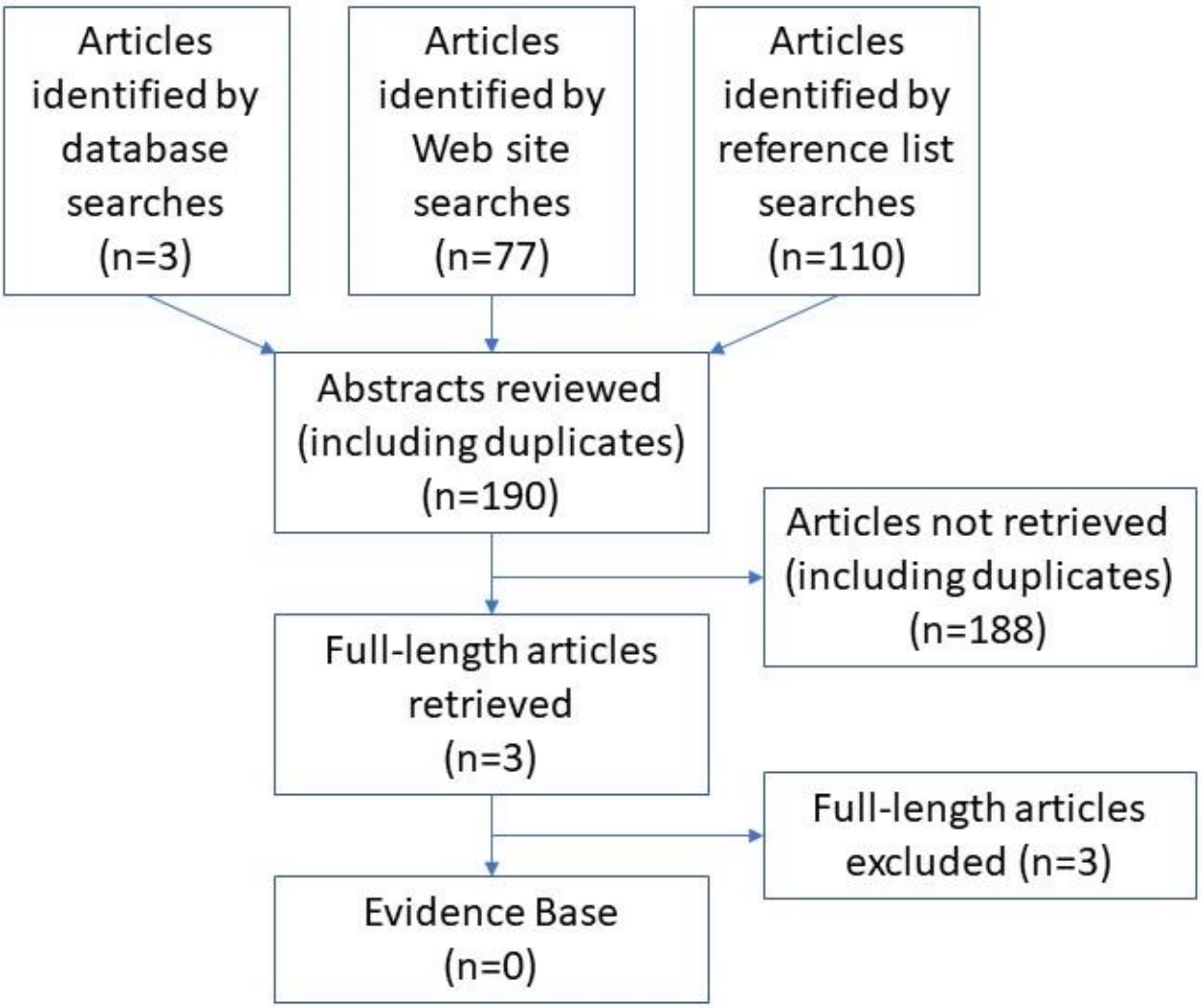
Possible risks for bias may stem from allocation concealment since randomization methods were unclear, as well as performance and detection bias due to lack of blinding. However, the inclusion of a control group limited the effect of these potential biases.

The evidence pertaining to the likelihood of seizure recurrence among individuals who have experienced a single unprovoked seizure is unacceptably weak. An insufficient evidence bases makes it difficult to draw conclusions on this topic.

Research Question 5

Evidence Base

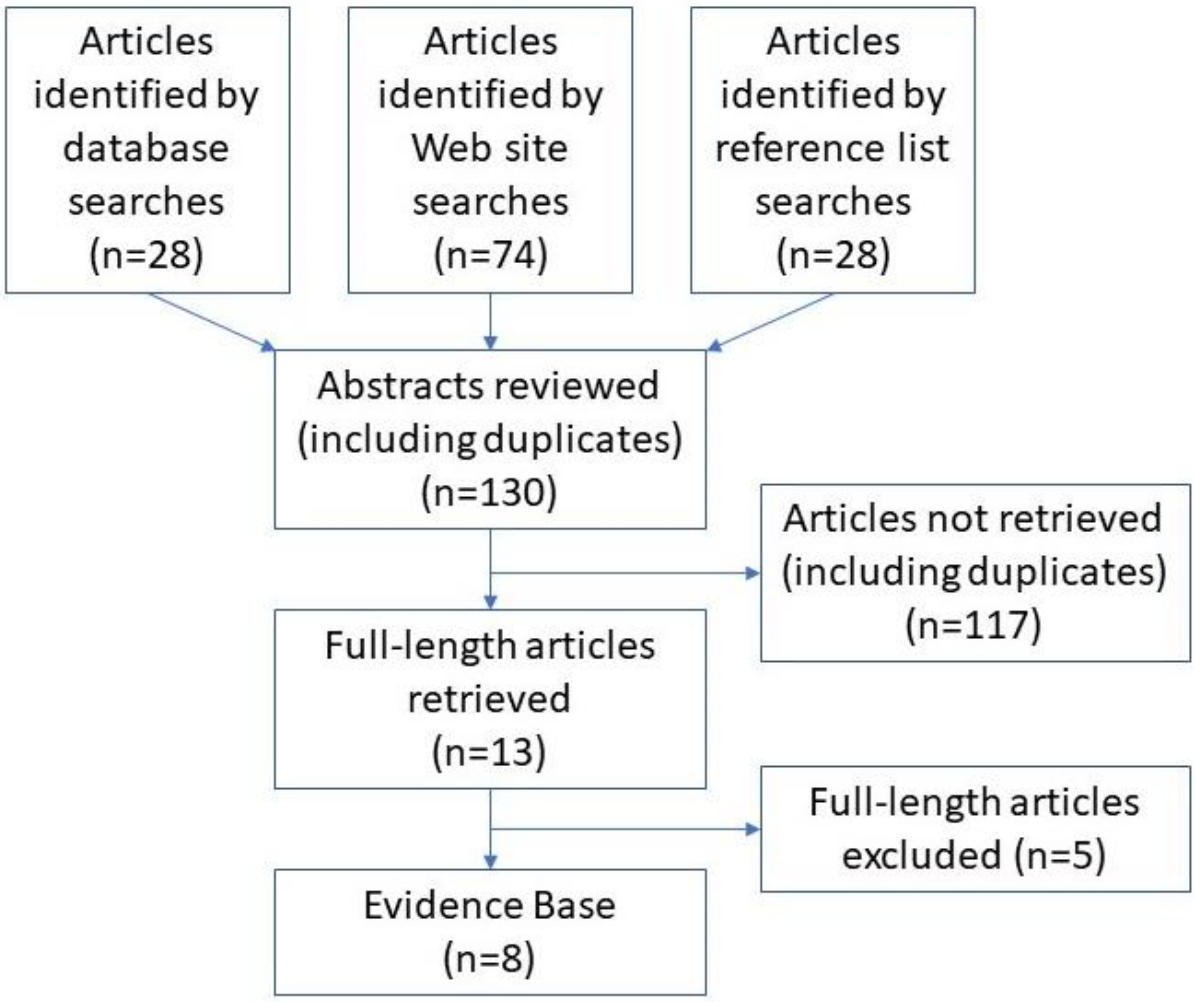
The evidence base for Question 5 consisted of n=0 studies, as shown in the search diagram.



Research Question 6

Evidence Base

The evidence base for Question 6 consisted of n=8 studies, as shown in the search diagram.



Summaries of Included Studies

#	Author	Year	Location of Study	Study Objective	Sample Size and Demographics	Study Design
1	de Groot, M., Douw, L., Sizoo, E.M., Bosma, I., Froklage, F.E., Heimans, J.J., Postma, T.J., Klein, M., Reijneveld, J.C.	2012	The Netherlands	Determine the effect of older and newer AEDs on cognitive performance in postoperative high-grade glioma patients	Cohort 1: n=33; Cohort 2: n=68; Cohort 3: n=32.	Cohort study
2	Elmosy, L., Bayoumy, A., Hafez, M., El Bialy, R., Imam, H., Imam, B.	2013	Egypt	Evaluate the effect of epilepsy on cognitive functions and quality of life in females using AEDs	30 Females (15 with focal epilepsy and 15 with generalized epilepsy)	Case Control

#	Author	Year	Location of Study	Study Objective	Sample Size and Demographics	Study Design
3	Hessen, E., Lossius, M.I., Reinvang, I., Gjerstad, L.	2007	Norway	Assess cognitive effects of anticonvulsants in a way that would yield results that are most directly-applicable to epilepsy populations	139 patients; no withdrawal group, n=75; mean age 37.2 (ranged 18-67); withdrawal group, n=64, mean age 39.2 (ranged 19-64)	Placebo-controlled, prospective, randomized, double-blind, parallel group study
4	Huang, C-W., Pai, M-C., Tsai, J-J.	2008	Taiwan	Study the comparative cognitive effects of levetiracetam (LEV) and toprimate (TPM) on intractable epilepsy (IE)	LEV Group: n=40 (18 female, 22 male), mean age 39.8 (SD 4.1); TPM Group: n=39 (16 femal, 23 male), mean age 38.8 (SD 3.4)	Non-randomized, blinded cognitive assessment, and parallel design

#	Author	Year	Location of Study	Study Objective	Sample Size and Demographics	Study Design
5	Kaussner, Y., Kenntner-Mabiala, R., Hoffmann, S., Klatt, J., Tracik, F., Krüger, H-P.	2010	Germany	Test the cognitive side effects of 900 mg/day of oxcarbazepine (OXC) as compared to 600 mg/day of carbamazepine (CBZ) with respects to driving	27; no demographic data reported	Double blind, randomized, crossover study
6	Lancman, M.E., Fertig, E.J., Tobliger, R.W., Perrine, K., Muyers, L., Iyengar, S.S., Malik, M.	2016	United States	Examine the cognitive and quality-of-life measures and outcomes with adjunctive lacosamide therapy in patients with treatment-resistant partial epilepsy?	34 patients (13 male, 21 female); mean age = 38.8 (SD=2.43 years)	Prospective, open-label, non-blinded, adjunctive therapy test-retest (within subjects)

#	Author	Year	Location of Study	Study Objective	Sample Size and Demographics	Study Design
7	Marimuthu P, Varadarajan S, Krishnan M, Shanmugam S, Kunjuraman G, Ravinder JR, Arumugam B, Alex D, Swaminathan P.	2016	India	Evaluate the effects of memantine on improving cognition and memory functions in epileptic patients with cognitive and memory impairement receiving AEDs.	Memantine group: n=26 (14 male, 12 female). Placebo group: n=29 (14 male, 15 female)	Randomized, double-blind, placebo-controlled, parallel design
8	Mills, K.C., Drazkowski, J.F., Hammer, A.E., Caldwell, P.T., Kustra, R.P., Blum, D.E.	2007	United States, Canada	Compare the effects of lamotrigine (LTG) with those of topiramate (TPM) as adjunctive therapy in adult patients with partial seizures.	67 adult patients; LTG group, n=35, 69% male, mean age=40.7; TPM group, n=32, 32% male	Randomized, double-blind study

Quality of Included Studies

#	Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Other bias
1	de Groot, M., Douw, L., Sizoo, E.M., Bosma, I., Froklage, F.E., Heimans, J.J., Postma, T.J., Klein, M., Reijneveld, J.C.	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk
2	Elmosy, L., Bayoumy, A., Hafez, M., El Bialy, R., Imam, H., Imam, B.	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk
3	Hessen, E., Lossius, M.I., Reinvang, I., Gjerstad, L.	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
4	Huang, C-W., Pai, M-C., Tsai, J-J.	High risk	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk	Unclear Risk
5	Kaussner, Y., Kenntner-Mabiala, R., Hoffmann, S., Klatt, J., Tracik, F., Krüger, H-P.	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
6	Lancman, M.E., Fertig, E.J., Tobliger, R.W., Perrine, K., Muyers, L., Iyengar, S.S., Malik, M.	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk

7	Marimuthu P, Varadarajan S, Krishnan M, Shanmugam S, Kunjuraman G, Ravinder JR, Arumugam B, Alex D, Swaminathan P.	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
8	Mills, K.C., Drazkowski, J.F., Hammer, A.E., Caldwell, P.T., Kustra, R.P., Blum, D.E.	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk

Findings

While only two of the included studies included measurement and assessment of AED use on simulated driving performance, all the studies measured and assessed the impact of AEDs on cognitive functions that can be considered as surrogate markers of driving safety. There was little agreement between or among study findings, with some studies observing cognitive impairment linked to AED use and others observing that AEDs were linked to improvement to, or maintenance of, cognitive function. This may be partly explained by the differing designs, methods, and goals of the various studies.

Kaussner et al., 2010 [5] and Mills et al., 2007 [8] both looked specifically at the effects of AEDs (oxcarbazepine and carbamazepine in Kaussner, and lamotrigine and topiramate in Mills) on simulated driving performance in healthy subjects. Kaussner employed both a simulator test and a self-assessment in which subjects reported on their performance, their effort, attention, and sleepiness. The researchers found that both drugs had a negative impact on driving performance, specifically on lane-keeping performance, incidence of driving mistakes, increased sleepiness, and lower self-assessment ratings. Negative effects were particularly noticeable during monotonous simulated scenarios. Performance was slightly less impacted for subjects in the oxcarbazepine group (900 mg/day), leading researchers to determine that it may be a more appropriate drug for epileptic patients who need to drive. Because this study involved healthy subjects, it is difficult to generalize the findings to CMV drivers or drivers with recurrent epilepsy.

Mills employed Performance On-Line, a computer-based system that measured scanning, divided attention, and effective field of view; a battery of standard cognitive assessments was also administered. Findings indicated that adjunctive topiramate (with a target dose of 300 mg/day) negatively impacted cognition and compromised target identification and attention

in the POL when compared with lamotrigine. Researchers compared the relative drug impairment to the observed impairment of alcohol (measured at 0.45%) or a 0.5mg dose of alprazolam. It should be noted, however, that while this study was a randomized, double-blind design, the study was funded by the manufacturer of lamotrigine, and that several members of the research team worked or consulted for that firm.

Elmosy et al., 2013 [2] also found generally negative impacts on cognition associated with AED use. Elmosy studied 30 females with epilepsy receiving either valproic acid or carbamazepine as monotherapy. Researchers measured and assessed cognitive function using P300 latency, a tool often employed for cognitive assessment in dementia studies, as well as the Mini-Mental State Exam (MMSE). Researchers found a prolonged latency and decreased amplitude of P300 in subjects in both drug groups, with no significant difference in the effect detected between the two drugs; additionally, there was a significant difference in MMSE results when compared with healthy control subjects. The researchers concluded that individuals with epilepsy experience a decline in cognitive function that is a result of their condition, AED therapy, or both, and that this results in a negative impact on their ability to engage in day-to-day activities. This study is limited, however, by its relatively small sample size, and its non-randomized or blinded design; additionally, it is difficult to generalize to CMV drivers as it involved all female subjects.

Like Elmosy, Lancman et al., 2016 [6] did not find significant changes to cognition as a result of AED use. Lancman examined the cognitive impact of adjunctive lacosamide therapy (with a maximum dosage of 400 mg/day) in 34 patients. Physical and cognitive assessments, as well as patient seizure diaries, were used to measure and assess outcomes. Researchers found that mean seizure frequency decreased significantly from the baseline to the post-treatment examination (18 patients experienced at least a 50% reduction and 3 experienced total seizure freedom), and that no significant differences were observed in the composite scores of the cognitive tests. While the researchers concluded that lacosamide carried low risks of significant cognitive changes, there are several limitations. The study had a small sample size and was not designed as a randomized and placebo-controlled study. Additionally, half of the cognitive tests employed did not have alternate versions, so practice effects can introduce bias into the results.

Similar to Lancman, Huang et al., 2008 [4] found that study drugs (levetiracetam and topiramate) did not significantly affect cognitive outcome. This study included 79 subjects, adding one of the two study drugs to their existing AED regimen. Once titrated, doses were maintained as long as 52 weeks. Cognition was evaluated using the Cognitive Abilities Screening Instrument (CASI), administered before the study (T1) and after one year of treatment (T2). There were no significant differences in cognition between groups at either T1 or T2. Scores for the specific orientation domain of the CASI were lower at T2 for the topiramate group, though overall, there was no significant difference in cognition within

either group at T1 or T2. Like Lancman, researchers concluded that treatment did no significantly affect cognition; however, this study did find that levetiracetam may preserve cognitive performance. Also like Lancman, this study was not randomized, meaning that cognitive comparisons may be difficult to draw over time. Additionally, the CASI may not be a sensitive enough instrument to detect some cognitive changes.

Unique among the studies, Marimuthu et al., 2016 [7] observed improvement in both memory and cognitive function among its 55 subjects. In a randomized, double-blind, placebo-controlled parallel study, the effects of memantine hydrochloride (target dose of 10 mg/day) on memory and cognition were measured and assessed using the Wechsler Memory Scale and the MMSE. Compared with the placebo group, researchers found that there was a significant improvement in cognition in the memantine group, as well as a significant improvement in memory.

Also unique among the studies, Hessen et al., 2007 [3] assessed the cognitive effects of withdrawal form AEDs in 139 patients experiencing more than two years of seizure freedom under monotherapy. Designed as a placebo-controlled, prospective, randomized, double-blind, parallel group study, subjects were randomized to either active medication or a withdrawal dose, reduced at set increments through the study. An array of tests were used to assess learning and memory, attention and psychomotor speed, executive functions, motor coordination, and steadiness; these tests were administered at the start of the study and seven months following the start of withdrawal. Researchers found that drug withdrawal was associated with a significant improvement in verbal fluency and response inhibition under time pressure. While the researchers admit that the potential clinical impact of these improvements is difficult to determine, because the associated cognitive processes are important for many day-to-day activities, there may be a significant functional impact to the findings.

De Groot et al., 2012 [1] studied the effects of older and newer AEDs on cognitive performance in post-operative high-grade glioma patients. Designed to represent three distinct eras of AED therapy, this cohort study included 133 patients in three cohorts (phenytoin, valproic acid, and levetiracetam). Each cohort had identical neuropsychological assessments administered by trained psychometricians and included assessment in six cognitive domains: attention, executive functioning, verbal memory, psychomotor functioning, and verbal processing speed. Overall, researchers found that patients on older and newer AEDs performed equally well in assessments as those not receiving an AED, that those on valproic acid performed better than those on phenytoin, and those on levetiracetam performed better in the verbal memory domain than those not on an AED. There are several limitations to this research, however, primarily that it is difficult to generalize to CMV drivers or drivers with recurrent epilepsy, as it is focused on post-surgical preventative therapy for high-grade glioma patients. Additionally, there was no randomization of treatment, so bias

regarding choice of treatment may exist; additionally, the study was conducted using different cohorts, which may have introduced bias, though identical protocols were followed for each. The study also did not register seizure burden, the dosage range for each drug, and the serum level for each AED.

The evidence base regarding the chronic effect of AED treatment on surrogate markets of driver safety is unacceptably weak. Methodological weaknesses and contradictory findings make it difficult to draw conclusions on this topic.

Recommendations to FMCSA

Amount of Evidence

A total of n=52 relevant research studies were identified for this study. We believe this is a sufficient amount of evidence to address FMCSA's research questions.

Appendices

Works Cited (Included Studies)

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