

The Humanistic and Economic Burden of Pediatric Focal Seizures in the United States

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Abstract

Objective: To better understand the humanistic and economic burden of focal seizures in children 2-12 years old. **Methods:** We conducted a targeted literature review by searching MEDLINE for English-language publications reporting on children 2-12 years old with focal seizures published in the United States since 2008. **Results:** Thirty-five publications were included. Incidence of focal seizures was 23.2 to 47.1 per 100,000 children per year; prevalence was 2.0 per 1,000 children, and ranged from 1.6 - 2.6 per 1,000 in patients of any age. Life expectancy was 47.3-61.8 years among children 3-12 years old. Patients took several antiepileptic drugs and experienced frequent seizures, sleep disorders, mood disorders, migraine, and seizure-related injuries (eg, bone fractures, sprains, open wounds). Children with focal seizures scored below average on cognitive assessments and up to 42%, 16%, and 19% had depression, anxiety, and attention-deficit disorder, respectively. Patients of any age had about 10 outpatient visits (2 epilepsy-related), 2 inpatient visits (less than 1 epilepsy-related), and 24 procedures (1 epilepsy-related) per year. Medication adherence was low: only half of pediatric patients maintained $\geq 90\%$ adherence over 6 months. Annual total health care costs among patients of any age ranged from \$18,369 - 38,549; first-year total health care costs for children were \$19,883. **Conclusions:** Incidence and prevalence of focal seizures is high and the humanistic and economic burdens are significant. Future studies focused exclusively on children with focal seizures are needed to more precisely describe the burden. We also suggest further research and implementation of methods to improve medication adherence as an approach to lessen burden on these young patients.

Keywords

literature review, epilepsy, focal seizures, child, incidence, prevalence, morbidity, utilization, adherence, quality of life

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Epilepsy is a chronic disorder characterized by recurrent, unprovoked seizures. The prevalence of epilepsy in the pediatric age group has been steadily increasing in the United States, where an estimated 470,000 children are living with epilepsy.¹ Focal or localization-related seizures originate in networks limited to one hemisphere and are the most common seizure type in all age groups, accounting for more than 50% of all seizures in children² and 20% to 66% of epilepsy in adults.³

Pediatric epilepsy is associated with significant humanistic burden on patients and their families, affecting their quality of life. In a review of incidence, prevalence, and the burden associated with epilepsy in the United States, epilepsy was found to be significantly associated with mood disorders (eg, depression, anxiety, attention-deficit hyperactivity disorder [ADHD]), cognitive and social burdens (eg, developmental delay, autism, repeating school grades, poorer social competence), other comorbidities (eg, headaches), and an increased risk for unmet medical and mental health needs.⁴ Further, a

multinational systematic review of qualitative studies on patients with all epilepsy types demonstrated the considerable mental toll the neurologic condition caused patients, resulting in a decreased quality of life.⁵

We conducted a review of existing literature to better understand the humanistic and economic burden of focal seizures in children 2-12 years old. Recent reviews on the burden of

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epilepsy have focused on general populations by including studies of patients of all ages or all epilepsy types.⁵⁻⁷ However, different seizure classifications help inform mortality and comorbidity risk, and the specificity is critical for research and therapy choice.⁸ Thus, in this review we focused on a specific seizure type (focal seizures).

Furthermore, the age of patients can also inform etiology, burden, and treatment choices.⁹ As a result, we focused on children, and used the International League Against Epilepsy (ILAE) definition of children as those older than 2 years and less than 12 years old.⁹ The rationale for the lower age cutoff is that some epilepsy types, such as benign familial infantile epilepsy, which are classified in and representative of the infant age range, often resolve by 2 years of age. That being said, considering the limited literature on the topic, we did not exclude literature that included age ranges outside of 2-12-year-old patients. In some cases, the best quality evidence that included our 2-12-year-old age range was not stratified by age and was composed of a broader age range, such as all patients under 65 years of age.

Other reviews presented findings only on a specific syndrome (such as Dravet Syndrome or Lennox-Gastaut Syndrome),^{10,11} the efficacy of specific treatments,^{12,13} or specific outcomes (such as literacy and language).^{14,15} We aimed to capture a comprehensive understanding of focal seizures by examining a wide range of outcomes, including incidence and prevalence, humanistic outcomes (mortality, morbidity, quality of life), and economic outcomes (health care utilization, health care costs). Further, given the potential to lessen the burden of focal seizures by improved adherence to treatment regimens, we reviewed the evidence for medication adherence in this patient population.

Methods

We searched MEDLINE (via PubMed) on August 1, 2018, to identify studies written in English published in the last 10 years that presented data collected within the US that included findings on children 2-12 years old with focal seizures or generalized tonic-clonic seizures and presented at least one outcome of interest (incidence, prevalence, mortality, morbidity, quality of life, health care utilization, health care costs, or medication adherence). MeSH and text words associated with epilepsy (eg, "epilepsy," "seizure disorder," "epilepsies, partial," "epilepsy, generalized," "epilepsy, tonic-clonic," "epileptic syndromes"), children (eg, "child," "child, preschool," "pediatrics"), and each outcome of interest were used. See Supplemental Material for full search string. Researchers experienced in literature reviews screened articles in two phases: an initial title and abstract screen followed by a full-text screen. Articles that stratified data by seizure type (focal seizures and/or generalized tonic-clonic seizures), presented data on a study population that included children 2-12 years old (even if data were grouped with patients of other ages), and were not studies of pharmacokinetics/pharmacodynamics, case series, or in vitro studies were included. We conducted the review using DistillerSR, a systematic review program (Evidence Partners, Ottawa, Canada). We abstracted data on each outcome of interest from included articles.

Only results from studies that included data on focal seizures are described in this review. There are several specific types of focal seizures, defined by clinical signs and symptoms (eg, motor, sensory, autonomic) or seizure origin (eg, temporal lobe epilepsy or extratemporal lobe epilepsy). Focal seizures without impaired awareness were previously referred to as simple partial seizures; focal seizures with impaired awareness were previously called complex partial seizures.^{8,9} In the results below, we use the names of the types of focal seizures that authors used in their studies.

Results

Our MEDLINE search yielded 3,020 records. Figure 1 illustrates the number of articles screened during each phase and reasons for exclusion. After the 2 screening phases, 35 studies presented findings on children 2-12 years old with focal seizures (although many grouped children this age with other age groups) and were included in this review. Below we describe those articles (Table 1). The most common outcome of interest was morbidity (16 studies), followed by quality of life (7 studies), prevalence (5 studies), and medication adherence (5 studies). Four studies were found on health care utilization, 3 on health care cost, 3 on mortality, and 2 on incidence.

Incidence and Prevalence

No studies presented incidence or prevalence rates of focal seizures for children 2-12 years old only. Instead, our review includes studies that presented data among children 2-12 years old grouped with patients of other ages. Using data from the Rochester Epidemiology Project, representing residents of Olmstead County, Minnesota, the incidence rates of focal seizures per 100,000 children by age group were 47.1 for ages 1-4 years, 36.0 for ages 5-8 years, and 23.2 for ages 9-12 years.⁴⁷ Using the same data set, another study exploring the familial risk of epilepsy estimated the standard incidence ratio of focal seizures among 1,239 first-degree relatives of any age (including children 2-12 years old) to be 2.6.³⁴

Using patient records from hospitals, clinics, and physician offices in rural Kansas counties, one study reported the prevalence of localization-related epilepsy to be 2.0 per 1,000 children aged 1 month to 17 years.²⁷ Using a similar method, the prevalence of focal seizures was 1.6 among patients of any age (including children 2-12 years old).³² A study using the Thomson Medstat MarketScan Commercial Insurance Database identified 79,149 patients under age 65 with partial onset seizures (POS), equivalent to approximately 2.6 per 1,000 commercially insured individuals in the United States. Although the prevalence rate in children was not reported, 29.16% of the sample with POS were patients aged <17 years.⁴² Eleven percent of the population aged <65 years with POS in this study were classified as refractory. A single-center study that evaluated seizures on prolonged video electroencephalography (EEG) in patients aged 0-20 years found partial seizures to be the primary events in 24.9% of admissions to the pediatric epilepsy monitoring unit.³⁵ Using National Inpatient Sample (NIS) data of patients aged <65 years, one study estimated the

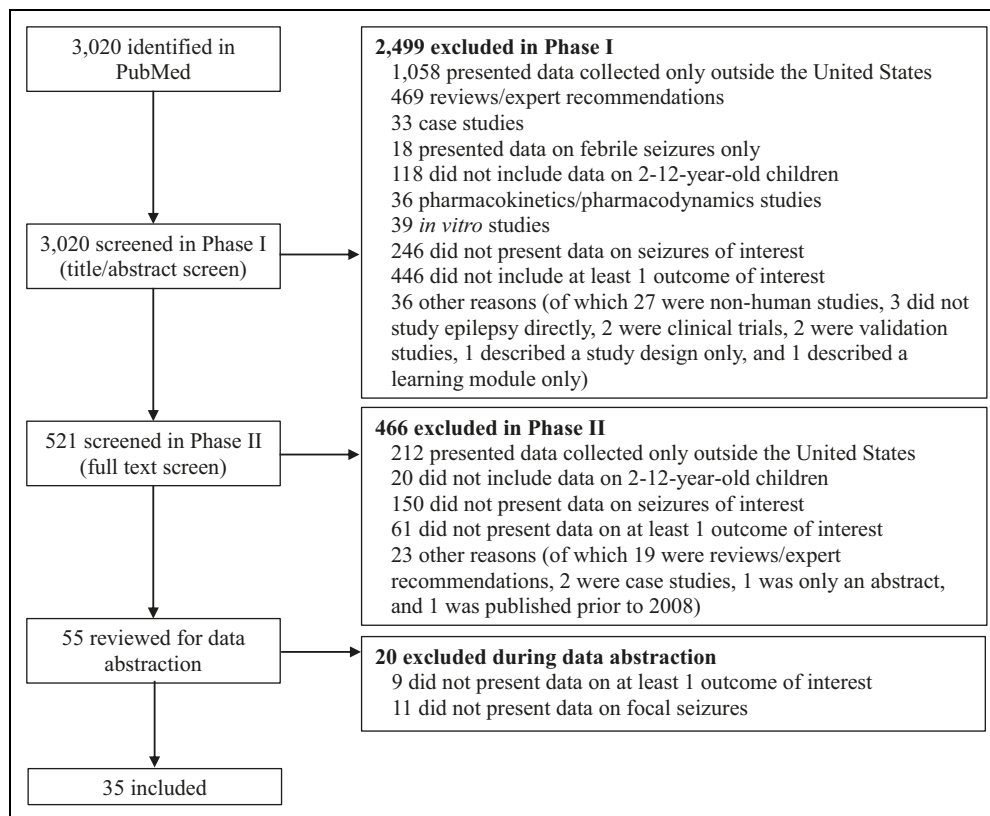


Figure 1. Screening Flow Chart .

number of focal-intractable epilepsy discharges over time (28,617 during 1998-2003; 40,425 during 2004-2009).⁴¹ Another study screened residents of any age along the Arizona-Mexico border to identify rates of lifetime and active epilepsy per 1,000 residents (14.32 for all lifetime epilepsy, 77.22% of which were localization-related; 11.82 for active epilepsy, 79.50% of which were localization-related).³⁷

Humanistic Burden

Mortality. No studies reported specifically on national or regional mortality rates in children. One study modeled remaining years of life expectancy in children 3-12 years old with 2 types of focal epilepsies (temporal lobe epilepsy and extratemporal lobe epilepsy) using medical management or surgical interventions.³⁰ With either treatment strategy, life expectancy was significantly shortened for these patients (among children with temporal lobe epilepsy: 47.3-56.0 years with medical management, 53.3-61.8 years with surgery; among children with extratemporal lobe epilepsy: 47.3-56.0 years with medical management, 52.9-61.6 with epilepsy surgery).³⁰ Two other studies reported mortality in pediatric cohorts <17 years old. One reported 69 deaths (3.1%) among 2,229 children with early-onset epilepsy, 33 of which (1.5% of all deaths) occurred in children with focal epilepsy.³⁶ The second study reported 5 deaths (11.9%) among 42 children with

early-onset focal epilepsy during the study period (1980-2009).⁴⁰

Morbidity, Seizure Frequency, and Medication Burden. Morbidity studies emphasized the significant humanistic burden facing this population, including that children who suffer from frequent seizures are required to take multiple medications and suffer from many comorbidities. Five studies reported on seizure frequency. Approximately half of patients 3-22 years old with Rolandic epilepsy (a less severe form of focal epilepsy) reported fewer than 6 seizures in their lifetime and half reported 6 or more.³¹ Focusing on children 6-16 years old, another study found that 46.7% with temporal lobe epilepsy and 36.7% with frontal lobe epilepsy (FLE) had seizures daily to weekly.²⁵ Patients 5-22 years old with intractable TLE stemming from a focal cortical dysplasia who underwent excisional epilepsy surgery preoperatively experienced a mean of 15 daily seizures and 24% had a history of status epilepticus.²³ A study using decision analysis modeling predicted that 10-year-old patients with either refractory temporal lobe epilepsy or extratemporal lobe epilepsy would experience 7.2 years of seizure freedom with medical management versus 26.7 (temporal lobe epilepsy) or 23.3 (extratemporal lobe epilepsy) years with surgical intervention.³⁰ In a study that followed up with patients a mean of 26 years after epilepsy-related surgery, 48.3% of patients with either complex partial or focal motor seizures had achieved Engel class I status (seizure freedom), and 9.2%, 20.8%, and

Table 1. Articles Included in This Review.

First author, journal, year	Title	Study design	Data source	Study population	Study period	Outcome of interest	Study population limitations
Liu, <i>J Child Adolesc Psychopharmacol</i> , 2018 ⁶	Stimulants Do Not Increase the Risk of Seizure-Related Hospitalizations in Children With Epilepsy	Claims analysis	Patient records in the Medicaid Analytic eXtract files	73,083 children 3-18 y old with epilepsy (defined as 2+ outpatient claims for epilepsy [ICD-9 code] at least 30 d apart over 2 y)	1999-2010	Healthcare utilization	3-18-y-olds
Schraegle, <i>J Int Neuropsychol Soc</i> , 2018 ¹⁷	Executive Dysfunction and Depression in Pediatric Temporal Lobe Epilepsy: The Contribution of Hippocampal Sclerosis and Psychosocial Factors	Prospective study	Children referred for epilepsy treatment at a tertiary care health system (details not provided)	62 children 8-16 y old with a prior diagnosis of TLE; all were candidates for surgery or experiencing cognitive difficulties	Not stated	Morbidity, quality of life	8-16-y-olds
Smith, <i>Epilepsia</i> , 2018 ⁸	PCDH19-Related Epilepsy Is Associated With a Broad Neurodevelopmental Spectrum	Retrospective chart review	Participants enrolled in the PCDH19 Registry, a repository of data collected from individuals with PCDH19-related epilepsy, established by the Boston Children's Hospital Epilepsy Genetics Program	17 patients 2-12 y old with PCDH19-related focal epilepsy	2014-2017	Morbidity	Study strength: All children 2-12 y old Only among those with PCDH19-related epilepsy
Schraegle, <i>Epilepsy Behav</i> , 2017 ⁹	The Relationship of Seizure Focus With Depression, Anxiety, and Health-Related Quality of Life in Children and Adolescents With Epilepsy	Prospective study	Patients referred to a pediatric neuropsychology service as a part of a comprehensive care program for epilepsy	132 children 6-18 y old with epilepsy	Not stated	Morbidity, quality of life	6-18-y-olds
Whealy, <i>Pediatr Neurol</i> , 2017 ²⁰	Prevalence and Risk Factors of Peri-ictal Autonomic Changes in Children With Temporal Lobe Seizures	Retrospective chart review	EEG reports of patients admitted to the Pediatric Epilepsy Monitoring Unit at the Mayo Clinic in Rochester	49 children 1 mo to 20 y old who experienced at least 1 EEG-confirmed seizure of temporal lobe onset with clinical features	2009-2013	Morbidity	1-mo to 20-year-olds
Fallah, <i>Epilepsy Behav</i> , 2016 ²¹	Cost-Utility Analysis of Competing Treatment Strategies for Drug-Resistant Epilepsy in Children With Tuberos Sclerosis Complex	Budget impact model	Literature obtained from MEDLINE search 2000-2015 for articles relevant to probabilities of interest applied to hypothetical patients treated at a tertiary care hospital	Hypothetical patients: children <18 y old with focal drug-resistant epilepsy secondary to tuberous sclerosis complex, amenable to surgery, failed to improve with 2 first-line AEDs	2000-2015	Healthcare costs	<18-y-olds
Love, <i>Epilepsy Behav</i> , 2016 ²²	The Role of Executive Functioning in Quality of Life in Pediatric Intractable Epilepsy	Prospective study	Patients referred for baseline neuropsychological evaluations for purposes of presurgical planning at a Florida hospital	54 children 6-18 y old with intractable epilepsy	Not stated	Quality of life	6-18-y-olds

(continued)

Table 1. (continued)

First author, journal, year	Title	Study design	Data source	Study population	Study period	Outcome of interest	Study population limitations
Maulisova, <i>Epilepsy Behav</i> , 2016 ²³	Atypical Language Representation in Children With Intractable Temporal Lobe Epilepsy	Retrospective chart review	Records of patients undergoing excisional epilepsy surgery at Miami Children's Hospital	46 children 5.5-22 y old with a confirmed diagnosis of TLE	1999-2003	Morbidity, quality of life	5-22-y-olds
Modi, <i>Epilepsia</i> , 2016 ²⁴	A Pilot Randomized Controlled Clinical Trial to Improve Antiepileptic Drug Adherence in Young Children With Epilepsy	Randomized controlled trial	Patients receiving care from the New Onset Seizure Clinic at Cincinnati Children's Hospital Medical Center	50 families of children 2-12 y old with new-onset epilepsy (defined as diagnosed within the last 7 mo), no comorbid chronic illnesses requiring daily medication, on AED medication, no prior AED treatment	2011-2012	Medication adherence	Study strength: All children 2-12 y old
Schraegle, <i>Epilepsy Behav</i> , 2016 ²⁵	List-Learning and Verbal Memory Profiles in Childhood Epilepsy Syndromes	Cross-sectional study	Children receiving care at the Comprehensive Epilepsy Program at Dell Children's Medical Center of Central Texas	90 children 6-16 y old with a diagnosis of TLE, FLE, or childhood absence epilepsy	Not stated	Morbidity, quality of life	6-16-y-olds
Veenstra, <i>Epilepsy Behav</i> , 2016 ²⁶	The Impact of Bilingualism on Working Memory in Pediatric Epilepsy	Retrospective chart review	Records of patients from the Children's Hospital of Orange County partnering hospitals, clinics, or doctor's offices in 9 rural Kansas counties	52 children 6-18 y old with focal or generalized epilepsy (26 bilingual and 26 controls)	2006-2015	Quality of life	6-18-y-olds
Hawley, <i>Epilepsy Behav</i> , 2015 ²⁷	Prevalence of Pediatric Epilepsy in Low-Income Rural Midwestern Counties	Retrospective chart review	Records of patients from 18 partnering hospitals, clinics, or doctor's offices in 9 rural Kansas counties	42,897 children 1 mo to 17 y old	2009	Prevalence	1-mo- to 17-y-olds
Pestana Knight, <i>Epilepsia</i> , 2015 ²⁸	Increasing Utilization of Pediatric Epilepsy Surgery in the United States Between 1997 and 2009	Claims analysis	Patient records in the Kids' Inpatient Database	375-706 children (depending on year) <18 y old with epilepsy (defined as having at least 1 ICD-9 code for epilepsy from 1997 to 2009)	1997-2009	Health care utilization	Less than 18-y-olds
Ryan, <i>Neurology</i> , 2015 ²⁹	Health Care Charges for Youth With Newly Diagnosed Epilepsy	Retrospective chart review	Records of patients from the New Onset Seizure Clinic at a large pediatric hospital serving patients in the Midwestern United States	258 children 2-18 y old diagnosed with epilepsy during study period who received 12 mo of care in the New Onset Seizure Clinic	2011-2012	Health care costs	2-18-y-olds
Sánchez, <i>Epilepsia</i> , 2015 ³⁰	Pediatric Refractory Epilepsy: A Decision Analysis Comparing Medical Versus Surgical Treatment	Decision model	Literature obtained from MEDLINE search through December 2013 for English-language articles relevant to probabilities of interest	Hypothetical patients: children 3-21 y old with refractory epilepsy eligible for surgery	Using literature through December 2013	Mortality, morbidity	3-21-y-olds
Vega, <i>Epilepsy Behav</i> , 2015 ³¹	Risk Factors for Reading Disability in Families With Rolandic Epilepsy	Prospective study	Patients receiving care from US pediatric neurology centers in New York, New Jersey, Pennsylvania, Connecticut, Rhode Island, and Massachusetts; southeastern UK pediatric centers	108 children 3-22 y old from the US and UK with Rolandic epilepsy, onset between 3 and 12 years	US: 2004-2009 UK: 2009-2012	Morbidity, quality of life	3-22-y-olds from US and UK

(continued)

Table 1. (continued)

First author, journal, year	Title	Study design	Data source	Study population	Study period	Outcome of interest	Study population limitations
Ablah, <i>Epilepsy Res</i> , 2014 ³²	Prevalence of Epilepsy in Rural Kansas	Retrospective chart review	Records of patients from 9 hospitals, 10 clinics and doctors' offices, 1 nursing home from 2 rural counties in Kansas	404 patients (any age) with active epilepsy (defined as having a history of recurrent, unprovoked seizures and having at least 1 unprovoked seizure or having taken anticonvulsant medication within 5 years of 2008)	2008	Prevalence	Any age
Modi, <i>Neurology</i> , 2014 ³³	Early Pediatric Antiepileptic Drug Nonadherence Is Related to Lower Long-term Seizure Freedom	Prospective study	Patients receiving care from the New Onset Seizure Clinic at Cincinnati Children's Hospital Medical Center	99 children 2-12 y old with new-onset epilepsy, no comorbid conditions requiring daily medication, receiving at least 1 AED	2006-2013	Medication adherence	Study strength: All children 2-12 y old
Pelito, <i>Brain</i> , 2014 ³⁴	Familial Risk of Epilepsy: A Population-Based Study	Retrospective chart review (of population-based sample)	Patients in the Genetic Epidemiology of Seizure Disorders in Rochester study, part of the Rochester Epidemiology Project	660 residents (any age) of Rochester, Minnesota with incident epilepsy (defined as 2+ unprovoked seizures from 1935-1994) and 2439 of their first-degree relatives	2003-2008	Incidence	All ages
Arrington, <i>Epilepsy Behav</i> , 2013 ³⁵	Utility and Safety of Prolonged Video-EEG Monitoring in a Tertiary Pediatric Epilepsy Monitoring Unit	Retrospective chart review	Records of patients admitted to St Joseph's Hospital and Barrow Neurological Institute in Phoenix, Arizona	454 admissions of children 11 d to 20 y old with treatment-resistant epilepsy (220 of the admissions captured epileptic events)	2008-2010	Morbidity	11-d- to 20-y-olds
Berg, <i>Pediatrics</i> , 2013 ³⁶	Mortality Risks in New-Onset Childhood Epilepsy	Combined data sets (Connecticut: prospective study; Rochester: retrospective chart review (of population-based sample); Nova Scotia: Prospective, population-based; Netherlands: Prospective, regional)	Combined data from 4 pediatric cohort studies; 2 data sets from US and 2 non-US	US studies Connecticut: 608 children 1 mo to 16 y old with newly diagnosed epilepsy (defined as 2+ unprovoked seizures within study period) Rochester: 466 children 1 mo to 17 y old with newly diagnosed epilepsy (defined as 2+ unprovoked seizures or single seizure with brain injury) Non-US studies Nova Scotia: 686 children 1 mo to 16 y old with newly diagnosed epilepsy (defined as 2+ unprovoked seizures within study period) Netherlands: 469 children 1 mo to 16 y old with newly diagnosed epilepsy (defined as 2+ unprovoked seizures within study period)	Connecticut: 1993-1997 Rochester: 1980-2009 Nova Scotia: 1977-1985 Netherlands: 1988-1992	Mortality	Mortality data combines US and non-US studies 1-mo- to 17-y-olds

(continued)

Table 1. (continued)

First author, journal, year	Title	Study design	Data source	Study population	Study period	Outcome of interest	Study population limitations
Chong, <i>Epilepsy Res</i> , 2013 ³⁷	The Prevalence of Epilepsy Along the Arizona-Mexico Border	Population-based study	Household residents in 3 rural US Arizona-Mexico border counties (Cochise, Santa Cruz, Yuma)	15,738 residents (any age) screened	2006-2008	Prevalence	Prevalence per 1,000 for all epilepsies by age group
Jain, <i>J Child Neurol</i> , 2013 ³⁸	Obstructive Sleep Apnea and Primary Snoring in Children With Epilepsy	Retrospective chart review	Records of patients from the Cincinnati Children's Hospital	60 children (age range not stated, mean 8-10 y) with epilepsy and obstructive sleep apnea or snoring	2006-2010	Morbidity	Age range not stated
Modi, <i>J Pediatr Psychol</i> , 2013 ³⁹	Preliminary Feasibility, Acceptability, and Efficacy of an Innovative Adherence Intervention for Children With Newly Diagnosed Epilepsy	Randomized controlled trial	Patients receiving care from the New Onset Seizure Clinic at Cincinnati Children's Hospital Medical Center	30 families of children 2-12 y old with new-onset epilepsy (defined as diagnosis within the last 7 mo), no comorbid chronic illnesses requiring daily medication, receiving at least 1 AED	Not stated	Medication adherence	Study strength: All children 2-12 y old
Moseley, <i>Epilepsy Res</i> , 2013 ⁴⁰	Early Onset Epilepsy Is Associated With Increased Mortality: a Population-Based Study	Retrospective chart review (of population-based sample)	Records of patients in the Genetic Epidemiology of Seizure Disorders in Rochester study, part of the Rochester Epidemiology Project	467 children (any age) of Rochester, Minnesota with incident epilepsy (defined as 2+ unprovoked seizures) and with onset in the prior 12 mo	1980-2009	Mortality	<17-y-olds
Schiltz, <i>Epilepsy Res</i> , 2013 ⁴¹	Temporal Trends in Pre-surgical Evaluations and Epilepsy Surgery in the U.S. From 1998 to 2009	Cross-sectional study	Patients in the Nationwide Inpatient Sample, part of the Healthcare Cost and Utilization Project, maintained by the Agency for Healthcare Research and Quality	34,106 patients younger than 65 y old with epilepsy (defined as having an epilepsy-related primary ICD-9 code with mention of intractability)	1998-2009	Prevalence	<65-y-olds
Chen, <i>J Med Econ</i> , 2012 ⁴²	Antiepileptic drug Treatment Patterns and Economic Burden of Commercially Insured Patients With Refractory Epilepsy With Partial-Onset Seizures in the United States	Claims analysis	Patient records in the Thomson Medstat MarketScan Commercial Insurance Database	79,149 patients <65 y old with any medical claim for POS and continuous enrollment for at least 1 y during study period; 8714 of which were classified as having refractory epilepsy	2004-2008	Prevalence, morbidity, health care costs, medication adherence	<65-y-olds
Jain, <i>Acta Neurol Scand</i> , 2012 ³⁸	Obstructive Sleep Apnea in Children With Epilepsy: Prospective Pilot Trial	Prospective study and chart review	Patients receiving care from pediatric neurology clinics in Virginia Commonwealth University Hospital System in Richmond, Virginia, and the Neurological Institute of Thailand	84 children (age not stated) with epilepsy; 53 from the US site, 31 from the Thai site	2007-2008	Morbidity	Age not stated; US and Thai children included
Kelley, <i>Neurology</i> , 2012 ⁴³	Comorbidity of Migraine in Children Presenting With Epilepsy to a Tertiary Care Center	Cross-sectional study	Patients evaluated in either the pediatric neurology resident continuity clinic or pediatric epilepsy clinic at Johns Hopkins Hospital	400 children 3-17 y old with a history of at least 2 afebrile seizures	2010-2011	Morbidity	3-17-y-olds

(continued)

Table 1. (continued)

First author, journal, year	Title	Study design	Data source	Study population	Study period	Outcome of interest	Study population limitations
Mohammed, <i>Epilepsia</i> , 2012 ⁴⁴	Impact of Epilepsy Surgery on Seizure Control and Quality of Life: A 26-Year Follow-up Study	Retrospective chart review and qualitative study	Records of patients of Dr Sidney Goldring at Barnes/St Louis Children's Hospital	361 patients (any age) who were operated on by Dr Goldring for seizures poorly controlled by medication; 117 of which completed follow-up interviews to assess quality of life	1967-1990	Morbidity	Any age
Wirrell, <i>Epilepsia</i> , 2012 ⁴⁵	Predictors and Course of Medically Intractable Epilepsy in Young Children Presenting Before 36 Months of Age: A Retrospective, Population-Based Study	Retrospective chart review (of population-based sample)	Records of patients in the Genetic Epidemiology of Seizure Disorders in Rochester study, part of the Rochester Epidemiology Project	127 children 1 mo to 17 y old in Rochester, Minnesota with new-onset epilepsy (defined as 2+ unprovoked seizures) and with onset in the prior 36 mo	1980-2009	Morbidity	1-mo- to 17-y-olds
Modi, <i>JAMA</i> , 2011 ⁴⁶	Patterns of Nonadherence to Antiepileptic Drug Therapy in Children With Newly Diagnosed Epilepsy	Prospective study	Patients receiving care from the New Onset Seizure Clinic at Cincinnati Children's Hospital Medical Center	124 children 2-12 y old with new-onset epilepsy, no comorbid conditions requiring daily medication, receiving at least 1 AED	2006-2009	Medication adherence	Study strength: All children 2-12 y old
Wirrell, <i>Epilepsy Res</i> , 2011 ⁴⁷	Incidence and Classification of New-Onset Epilepsy and Epilepsy Syndromes in Children in Olmsted County, Minnesota From 1980 to 2004: A Population-Based Study	Retrospective chart review (of population-based sample)	Records of patients in the diagnostic indexes of Rochester Epidemiology Project	359 children 1 mo to 17 y old with new-onset epilepsy (defined as 2+ unprovoked seizures from 1980-2004)	1980-2004	Incidence	Incidence per 100,000 for 1-4-y-olds presented
Kurth, <i>Epilepsia</i> , 2010 ⁴⁸	Healthcare Resource Utilization in Patients With Active Epilepsy	Claims analysis	Patient records in the MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases	46,847 patients (any age) with any medical claim for epilepsy, at least 1 epilepsy-related health care resource use claim, and at least 6 mo of enrollment during the study period	2005-2007	Health care utilization	Any age
Roeder, <i>Epilepsia</i> , 2009 ⁴⁹	Depression and Mental Health Help-Seeking Behaviors in a Predominantly African American Population of Children and Adolescents With Epilepsy	Prospective study	Patients receiving care from an outpatient neurology clinic at the Children's Hospital of Michigan in Detroit	96 children 6-17 y old with a clinical diagnosis of epilepsy	Not stated	Morbidity, health care utilization	6-17-y-olds

Abbreviations: AED, antiepileptic drug; EEG, electroencephalography; FLE, frontal lobe epilepsy; POS, partial onset seizure; TLE, temporal lobe epilepsy.

21.7% were found to be Engel classes II, III, and IV, respectively.⁴⁴ Lastly, in a study of 0-17-year-old children with epilepsy onset prior to 3 years of age included in the Rochester Epidemiology Project database, patients with a nongeneralized mode of onset had higher odds of having medically intractable epilepsy.⁴⁵

Five studies reported on antiepileptic drug burden and show that antiepileptic drug burden increases with severity of epilepsy. In one study, 47% of 3-22-year-old patients with Rolandic epilepsy were on 1 antiepileptic drug.³¹ Another study reported that children 8-16 years old with temporal lobe epilepsy took a mean of 1.45 antiepileptic drugs.¹⁷ Two other studies found that more than half of children with temporal lobe epilepsy and FLE (56.7%-71.0%) were on antiepileptic drug polytherapy (defined as more than 1 antiepileptic drug).^{28,33} In a severe form of the condition, PCDH19-related focal epilepsy, 82% of 2-12-year-old children were on more than 3 antiepileptic drugs.¹⁸

Studies of adults and children illustrate that children with focal seizures suffer from high rates of comorbidities, especially mood disorders. Further, within the focal seizures population, those with refractory epilepsy have higher rates of mood disorders than those with nonrefractory epilepsy. Five studies reported on behavioral disorders and found high rates in patients with focal seizures. Depression was found in 12.0% to 41.5% of children 6-18 years old^{19,49} and 9.6% to 14.1% of all patients (including children) <65 years old (higher rates among refractory patients).⁴² Anxiety was reported in 16% of children 6-18 years old¹⁹ and 5.0% to 6.7% of all patients (including children) <65 years old (higher rates among refractory patients).⁴² In patients with PCDH19-related focal epilepsy, 23.5% patients had an autism diagnosis.¹⁸ In patients 3-22 years old with Rolandic epilepsy, 18.81% had ADHD.³¹

Studies also reported on sleep disorders, migraine, and injuries. Three reported on sleep disorders: 30.8-76.1% of children with focal epilepsy (age range not stated) had sleep apnea^{38,50} and 58.8% of children 2-12 years old with PCDH19-related focal epilepsy had "abnormal sleeping patterns."¹⁸ Two studies reported on migraine: one found 8.0% to 9.7% of patients <65 years old with POS had migraine (higher for refractory patients)⁴² and a second reported that Rolandic epilepsy was associated with migraine in patients 3-17 years of age.⁴³ Only 1 study reported on seizure-related injuries among patients any age with POS, with all rates being higher for refractory patients, including bone fractures (4.9%-6.5%), dislocations (2.5%-2.9%), sprains and strains (8.4%-10.0%), open wounds (5.0%-7.3%), and burns (0.5%-0.6%).⁴²

Cognitive Development and Quality of Life. Several studies used instruments to test children's cognitive development and quality of life. Studies used different instruments to test for language, reading, memory, motor, and visuospatial development delays and found that patients suffer from significant neurologic developmental delays. Instruments included the Delis-Kaplan Executive Function System (DKEFS),^{17,26} the California Verbal Learning Test-Children's Version

(CVLT-C),^{25,17} the Trail Making Tests,^{23,26} and the Behavior Rating Inventory of Executive Function (BRIEF).^{17,22} Four studies reported on patient IQ,^{17,23,22,26} two of which used the Wechsler Intelligence Scale for Children (WISC-IV). One reported low average scores (7.44-7.69 on verbal reasoning and 7.46-8.09 on spatial reasoning) among children 8-16 years old with temporal lobe epilepsy¹⁷ and the other found average general ability index and working memory index scores among children 6-18 years old with focal epilepsy.²²

Two studies reported on overall quality of life using the Quality of Life in Children Epilepsy Questionnaire (QOLCE),^{19,22} a test of five quality-of-life domains (physical, cognitive, social, and behavioral function and emotional well-being) designed for children with epilepsy. Scores are transformed linearly into scales of 0-100, with higher scores representing higher quality of life.⁵¹ In 6-18-year-olds with focal epilepsy, both studies found QOLCE scores to be low (approximately 57).^{19,22}

Economic Burden

Health Care Utilization. Yearly visits were not reported for the pediatric population. Using health care claims data to investigate patients of all ages with complex or simple partial seizures, one study reported on epilepsy-specific utilization (1.75-1.91 outpatient visits, 0.25-0.28 inpatient days, 0.04 emergency department visits, and 1.15-1.31 diagnostic tests and procedures) and all-cause health care utilization (10.03-10.42 outpatient visits, 1.76-1.81 inpatient days, 0.66 emergency department visits, and 23.54-24.66 diagnostic tests and procedures).⁴⁸ The same study reported higher utilization rates for patients diagnosed with epilepsy partialis continua, including epilepsy-specific utilization (1.67 outpatient visits, 1.04 inpatient days, 0.05 emergency department visits, and 1.48 diagnostic tests and procedures) and all-cause health care utilization (12.94 outpatient visits, 5.98 inpatient days, 0.99 emergency department visits, and 34.65 diagnostic tests and procedures). The qualifying diagnostic tests and procedures were identified through health care claims-based codes, which were not listed in the study.

The remaining three studies reported on unique health care utilization outcomes in the pediatric population. Using the Kids' Inpatient Database, one study reported on the percentage of patients aged <18 years with refractory focal epilepsy who had surgeries out of the estimated number who would have been expected to have surgeries, which ranged from 19.4% in 1997 to 34.5% in 2009.²⁸ Although surgical utilization increased over time, only one-third of those expected underwent a procedure in 2009. Another study found that less than one-third of 6-17-year-old children with focal epilepsy receiving care at an outpatient neurology clinic who screened positive for depression (29.63% of 27 children) sought mental health services.⁴⁹ The authors reported that denial of depression by parents was the reason for not seeking mental health care; no other barriers to care were mentioned in interviews. The third study compared the likelihood of hospitalizations among

children 3-18 years old with focal epilepsy who were current versus former users of stimulants. The authors found no difference in hospitalization rates between the 2 cohorts.¹⁶

Health Care Cost. Total all-cause first-year health care costs in children 2-18 years old with focal epilepsies were \$19,883.²⁹ Epilepsy-specific health care costs were not reported for the 2-12 year age group; in patients less than 65 years of age with POS, these ranged from \$3,126 to \$13,750 per year. All-cause costs ranged from \$18,369 to \$38,549 per year in patients <65 years old.⁴² Patients with refractory POS incurred higher epilepsy-specific and all-cause health care costs than those with nonrefractory epilepsy.

In a cost-utility analysis in a hypothetical cohort of children <18 years old with focal drug-resistant epilepsy secondary to tuberous sclerosis complex, the total 5-year health care costs were estimated to be \$6,568 for a third antiepileptic drug, \$13,459 for a ketogenic diet, \$50,743 for vagus nerve stimulator implantation, and \$73,384 for resective surgery.²¹

Medication Adherence

Five studies reported on treatment adherence or persistence, four of which used the same methodology in children 2-12 years old with new-onset epilepsy and were written by the same first author.^{24,33,39,46} In these studies, Modi et al defined adherence as the daily use of an antiepileptic drug monitored with a system that identifies when a pill bottle is opened and a pill is removed and defined adherence level slightly differently in each study, ranging from 90% to 95%.

The adherence rates in these studies spanned relatively short periods. In two of the four studies, Modi et al collected adherence over a 1-month period and found 73.33% of children with localization-related epilepsy had $\geq 90\%$ adherence³⁹ and 39.13% of children with localization-related epilepsy had $\geq 95\%$ adherence.²⁴ The 2014 study found 46.55% of children with localization-related epilepsy had $\geq 90\%$ adherence over a 6-month period.³³ The 2011 study did not provide a definition for "near-perfect adherence."⁴⁶ Instead, they used trajectory modeling based on 6 months of adherence data to group children into adherence-based groupings, and classified 37.83% of children with localization-related epilepsy into the "near-perfect adherence" group.

The remaining study described treatment patterns over a 4-year follow-up period in patients <65 years old with refractory POS. Authors reported that at baseline, 80.5% of patients were on monotherapy, 15.3% were on combination therapy, and 4.2% were on triple/quadruple therapy. Among those on monotherapy, about half (57.4%) added another antiepileptic drug and 42.6% switched antiepileptic drugs during the follow-up period. Among those on combination therapy, 41.6% added a third antiepileptic drug, 42.6% discontinued 1 antiepileptic drug, 10.9% switched 1 of the antiepileptic drugs, and 2.7% completely switched combinations during the follow-up period. Among those on triple/quadruple therapy, most

(70.0%) discontinued at least 1 of the antiepileptic drugs during the follow-up period.⁴²

Discussion

Our review of literature shows that focal seizures in US children, including those 2-12 years old, is associated with significant individual and societal burdens. Incidence (23.2-47.1 per 100,000 children 1-12 years old per year) and prevalence (2.0 per 1,000 children 1 month to 17 years old) of focal seizures are high, similar to that of type 1 diabetes and cerebral palsy in children.^{52,53} Children have shortened life spans (47.3-61.8 remaining years among children 3-12 years old), suffer from a number of comorbidities (mood disorders, sleep disorders, migraine, seizure-related injuries), and are developmentally delayed. The costs of focal seizures are high among patients of all ages: patients had 10 outpatient visits and 2 hospitalizations, and annual total health care costs ranged from \$18,369 to \$38,549. Medication adherence is low: the proportion of children 2-12 years old with focal seizures with high adherence decreased from 73.3% over 1 month to 46.6% over a 6-month period.

Using the first-year total health care cost for children with epilepsy of \$19,883²⁹ and the prevalence of focal seizures in children of 2.0 per 1000,²⁷ we estimate the yearly health care cost for pediatric focal seizures in the US to be \$2.9 billion.⁵⁴ One way to decrease these costs is to improve medication adherence. Low adherence rates to antiepileptic drugs in adults are associated with increased mortality, emergency department visits, hospitalizations, head injuries, and fractures.⁵⁵ Another study reported significantly greater resource use and costs in children with uncontrolled than controlled epilepsy.⁵⁶ Taken together, these studies support that increasing medication adherence, and therefore better controlling focal seizures, could also be associated with decreased costs.

The medication adherence studies described in this review followed patients 2-12 years old for up to 6 months, yet still reported low adherence rates (only half of pediatric patients achieved high adherence during the 6-month period).³³ The burden of low adherence is also documented in the study: non-adherent pediatric patients during the 6-month study period were 3.24 times more likely to not have achieved seizure freedom after 4 years.³³ Various strategies have been shown to improve medication adherence in epilepsy. Family-based adherence interventions such as those described in the Modi et al studies were associated with improved medication adherence.^{24,33} Additionally, a recent Cochrane review of interventions to improve medication adherence found that behavioral interventions like those described above had positive effects on adherence rates.⁵⁷

The burden of focal seizures extends to families and caregivers.^{10,11} Caring for children facing significant comorbidities, cognitive delay, and high costs is challenging. Moreover, medication adherence is the responsibility of a caregiver or parent for young children, adding further strain on parents or caregivers.

This review has limitations. First, many studies in this review included patients of all ages with focal seizures, not specifically patients 2-12 years old. Because of a lack of literature focused on patients 2-12 years old, we included all studies that contained data on children 2-12 years old, even if combined with other age groups. Second, studies that grouped all types of epilepsies together (as was often the case for studies that used health care claims data) were excluded. Specificity in epilepsy classification is needed to better quantify risks and treatment regimens. Similarly, because our aim was to find studies focused on focal seizures, we did not investigate the proportion of focal seizure patients among all children with epilepsy. In addition, few studies reported on similar outcomes or used similar measures, making it difficult to consolidate and summarize findings across studies. Lastly, we did not intend to conduct a systematic review and several limitations associated with the targeted nature of the search could have affected the type and number of studies included. For instance, we did not assess the quality of the studies included or whether any author bias was present. Individual reviewers screened studies and abstracted data, leading to potentially low (but untested) inter-rater reliability.

Epilepsy differs in children and adults; the effect of seizures on a developing brain results in more severe neuropsychological impact than adult-onset seizures.⁵⁸ Many studies in this review combined all age ranges of patients with focal seizures. Further, we found no studies reporting more severe consequences of focal seizures, such as rates of intensive care unit stays or status epilepticus. Additional research is needed exclusively on children 2-12 years old to further characterize the burden of focal seizures in this pediatric age group. For example, areas of further work could include better estimates of medication adherence, comparisons of utilization for extended-release to immediate-release medications, the use of Medicaid and commercial health care claims data to investigate utilization and cost among children only, investigations of indirect costs such as caregiver burden, and qualitative studies outside of the health care setting to assess the quality of life of patients, caregivers, and adults that suffered from epilepsy as children. This research will provide more precise evidence on the burdens experienced by this population and help to develop an understanding of how to improve the quality of life and health outcomes of these children. Lastly, given the significant humanistic and economic burden of focal seizures demonstrated in this review, we suggest further research and implementation of methods to improve medication adherence as an approach to lessen the burden on these young patients.

Our review presents a uniquely broad and recent overview of the burden of focal seizures in the US population of 2-12-year-old children. The incidence and prevalence of focal seizures are high, these children have a shortened life-expectancy, suffer from more comorbidities, and are developmentally delayed. Medication adherence to antiepileptic drugs remains low and health care costs are high. In our review, there was a scarcity of literature focused on the 2-12-year-old age range. To present results on all outcomes, we included studies that

incorporated 2-12-year-old children within a broader age range. Therefore, this review not only illustrates the significant burden facing these children, but also identifies areas of future work.

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Author Contributions

SNG, KAH, & IY contributed to study conception and design; data acquisition, analysis, and interpretation; drafted, critically revised, and approved final manuscript. IK & JC contributed to study conception and design; contributed to data interpretation; critically revised and approved final manuscript. ES contributed to data interpretation; critically revised and approved final manuscript.

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Supplemental Material

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