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SYSTEMATIC REVIEW

Management of Infantile Epilepsies

In Partnership with

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Management of Infantile Epilepsies

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

The American Epilepsy Society nominated this topic to the Patient-Centered Outcomes Research Institute® (PCORI®), which was established to fund research that helps patients and caregivers make better informed healthcare choices. To fulfill its authorizing mandate, PCORI partners with AHRQ to generate evidence synthesis products and make comparative effectiveness research more available to patients and providers.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Management of Infantile Epilepsies

Structured Abstract

Objectives. Uncontrolled seizures in children 1 to 36 months old have serious short-term health risks and may be associated with substantial developmental, behavioral, and psychological impairments. We evaluated the effectiveness, comparative effectiveness, and harms of pharmacologic, dietary, surgical, neuromodulation, and gene therapy treatments for infantile epilepsies.

Data sources. We searched Embase®, MEDLINE®, PubMed®, the Cochrane Library, and gray literature for studies published from January 1, 1999, to August 19, 2021.

Review methods. Using standard Evidence-based Practice Center methods, we refined the scope and applied a priori inclusion criteria to the >10,000 articles identified. We ordered full text of any pediatric epilepsy articles to determine if they reported any data on those age 1 month to <36 months. We extracted key information from each included study, rated risk of bias, and rated the strength of evidence. We summarized the studies and outcomes narratively.

Results. Forty-one studies (44 articles) met inclusion criteria. For pharmacotherapy, levetiracetam may cause seizure freedom in some patients (strength of evidence [SOE]: low), but data on other medications (topiramate, lamotrigine, phenytoin, vigabatrin, rufinamide, stiripentol) were insufficient to permit conclusions. Both ketogenic diet and the modified Atkins diet may reduce seizure frequency (SOE: low for both). In addition, the ketogenic diet may cause seizure freedom in some infants (SOE: low) and may be more likely than the modified Atkins diet to reduce seizure frequency (SOE: low). Both hemispherectomy/hemispherotomy and non-hemispheric surgical procedures may cause seizure freedom in some infants (SOE: low for both), but the precise proportion is too variable to estimate. For three medications (levetiracetam, topiramate, and lamotrigine), adverse effects may rarely be severe enough to warrant discontinuation (SOE: low). For topiramate, non-severe adverse effects include loss of appetite and upper respiratory tract infection (SOE: moderate). Harms of diets were sparsely reported. For surgical interventions, surgical mortality is rare for functional hemispherectomy/hemispherotomy and non-hemispheric procedures (SOE: low), but evidence was insufficient to permit quantitative estimates of mortality or morbidity risk. Hydrocephalus requiring shunt placement after multilobar, lobar, or focal resection is uncommon (SOE: low). No studies assessed neuromodulation or gene therapy.

Conclusions. Levetiracetam, ketogenic diet, modified Atkins diet, and surgery all appear to be effective for some infants. However, the strength of the evidence is low for all of these modalities due to lack of control groups, low patient enrollment, and inconsistent reporting. Future studies should compare different pharmacologic treatments and compare pharmacotherapy with dietary therapy. Critical outcomes underrepresented in the literature include quality of life, sleep outcomes, and long-term development.

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Executive Summary

Main Points

- Levetiracetam may cause seizure freedom in some patients, but data on other medications (topiramate, lamotrigine, phenytoin, vigabatrin, rufinamide, stiripentol) were insufficient to permit conclusions.
- Both the ketogenic diet and the modified Atkins diet may reduce average seizure frequency. The ketogenic diet may cause seizure freedom in some infants and may be more likely than a modified Atkins diet to reduce frequency.
- Both hemispherectomy/hemispherotomy and non-hemispheric surgical procedures may cause seizure freedom in some infants; however, the precise proportion is too variable to estimate. Surgical mortality for functional hemispherectomy/hemispherotomy and non-hemispheric procedures is rare. Hydrocephalus requiring shunt placement after multilobar, lobar, or focal resection is uncommon.
- No studies assessed neuromodulation or gene therapy.

Background and Purpose

Infantile epilepsies have serious short-term health risks and may lead to significant developmental, behavioral, and psychological impairments. However, treating seizures may have adverse effects that could also contribute to delayed development or reduced cognitive function. Thus, providers and caregivers must balance seizure control with the potential harms of treatment.

The three primary categories of treatment are pharmacotherapy, dietary treatments, and surgery. Wide practice variation, as well as newer modalities such as neuromodulation and gene therapy, suggest the need for a thorough evidence review. This systematic review was developed to support the American Epilepsy Society (AES) in potential development of a clinical practice guideline. However, the findings may also support decision making by parents and clinicians, as well as policy makers and funders of research.

Methods

We utilized standard methods of the Evidence-based Practice Center (EPC) program of the Agency for Healthcare Research and Quality (AHRQ). To refine Key Questions and the research protocol, we interviewed clinical Key Informants, our Technical Expert Panel (with multidisciplinary expertise), and we also consulted with AHRQ, the American Epilepsy Society, and the Patient Centered Outcomes Research Institute.

A professional information specialist searched four databases (MEDLINE, EMBASE, PubMed, and the Cochrane Library) for articles published from January 1, 1999 to August 19, 2021. The resulting >10,000 articles were imported into Distiller for screening by three systematic reviewers, who applied *a priori* study inclusion criteria to titles, abstracts, and full articles. These criteria focused on studies enrolling infants with epilepsy age 1 month to <36 months; we excluded studies of older children, neonates, and infantile spasms (West syndrome). Infantile spasms were excluded from this project because of distinctive biology, a well-defined evidence base, and resource constraints.

Forty-one studies (44 articles) met inclusion criteria, and we entered all critical information into evidence tables, including study design, country, funding source, study duration, sample size, eligibility criteria, population characteristics, clinical conditions, intervention(s), concomitant treatment(s), comparator(s), and results. We discussed all included studies narratively, and we rated the strength of evidence (SOE) using EPC methods for a list of prespecified critical outcomes (see full descriptions in the main report).

Results

Twelve studies (two randomized controlled trials [RCTs], three non-randomized comparative studies, and seven pre/post studies) met inclusion criteria for the effectiveness of pharmacologic treatments. Two studies of levetiracetam reported seizure freedom rates, and both support the conclusion that levetiracetam may cause seizure freedom in some infants (SOE: Low). Studies of topiramate, lamotrigine, phenytoin, vigabatrin, rufinamide, and stiripentol were insufficient to reach a conclusion. Regarding comparative effectiveness, one nonrandomized comparative study found that the chance of freedom from monotherapy failure was greater with levetiracetam than with phenobarbital. Another nonrandomized study compared topiramate with carbamazepine, but the data were inconclusive.

Twenty-four studies (2 RCTs of diet, 6 pre/post studies of diet, and 16 pre/post studies of surgery) met inclusion criteria for the effectiveness of non-pharmacologic treatments (e.g., dietary therapies, surgery, and neuromodulation). For ketogenic diet (KD), all 7 studies (2 RCTs and 5 pre/post studies) support the conclusion that KD may cause seizure freedom in some infants (SOE: Low). Two RCTs support the conclusion that a modified Atkins diet (MAD) may reduce seizure frequency (SOE: Low). Further, two RCTs comparing KD with MAD suggest that KD may cause greater reductions in seizure frequency (SOE: Low). No other dietary interventions met our inclusion criteria.

Sixteen retrospective pre/post studies of surgical interventions reported effectiveness outcomes of operations performed from 1979 to 2020. Studies reported outcomes for the following procedures: hemispherectomy/hemispherotomy (n=12), non-hemispheric procedures (such as intralobar, lobar, or multilobar resections and focal cortical resections, n=8), and tumor resection (n=1). Both hemispherectomy/hemispherotomy and non-hemispheric surgical procedures cause seizure freedom in some infants (SOE: Low); however, the precise proportion is too variable to estimate. The study of tumor resection was inconclusive (SOE: Insufficient). Because indications for specific surgical procedures differ by patient, we did not attempt to compare patient outcomes after different surgical procedures.

No included studies compared surgical interventions to other treatment modalities (e.g., pharmacologic or other adjunctive treatment).

Twelve studies of pharmacologic interventions, four studies of dietary treatments, and 12 studies of surgery met inclusion criteria for our examination of treatment harms. Only pharmacotherapy studies collected and reported harms systematically. We concluded that for three medications (levetiracetam, topiramate, and lamotrigine) adverse effects are rarely severe enough to warrant discontinuing medication (SOE: Moderate for topiramate, and Low for the other two). For topiramate, we found consistent evidence of dose-response effects for two non-severe adverse effects (SOE: Moderate): loss of appetite and upper respiratory tract infection. For dietary treatments, evidence on adverse effects was insufficient to permit conclusions. For surgical interventions, based on eight studies after functional hemispherectomy/hemispherotomy

and 4 studies of other non-hemispheric resective procedures (such as multilobar, lobar, or focal resections) we concluded that mortality after these procedures is rare (SOE: low).

Strengths and Limitations

Strengths of the review include an exhaustive search for any evidence on infants 1 month to less than 36 months, including a laborious search for pertinent subgroup analyses in pediatric studies; almost a third of our evidence could only have been identified with this level of scrutiny. We also employed relatively lenient inclusion criteria in order to summarize all pertinent evidence. Limitations include the lack of control groups in most studies, exclusion of evidence prior to 1999 (which may have excluded some relevant studies), sparse data which precluded analyses of specific etiologies or seizure types, no included data on the cost of treatments, and the variability of surgical interventions across time and centers.

The low number of RCTs or even nonrandomized comparative studies for many interventions lowers the strength of evidence for those interventions. This issue is especially true for surgical interventions; all of the articles included for surgical interventions were pre/post studies (case series).

Implications and Conclusions

Studies generally focused on seizure freedom and seizure frequency, and few reported other important outcomes such as hospitalization, neurodevelopment, infant/caregiver quality of life, sleep outcomes, and functional performance. Further, reported outcomes often use different metrics and units. Some standardized outcomes do exist, such as the Engel classification of surgical outcomes, but are not consistently used across studies. We suggest that future research measure more patient-oriented outcomes (such as those listed above) and use any existing standardizations of those outcomes.

No studies have compared pharmacotherapy with dietary or surgical treatments, a key target for future research. Epilepsy presents a different challenge at different age groups, particularly among infants with different epilepsies. Use of clear age cut-offs to demarcate this population in future studies will support future analysis by researchers and clinical policy makers. In general, evidence on the management of infantile epilepsies is weak, and better-quality research in the future could guide decision-making of both clinicians and parents.

Introduction

Background

Seizures are episodes of abnormal electrical activity in the brain, which can manifest clinically in various forms. Epilepsy is a disease characterized by an enduring predisposition to epileptic seizures and the neurobiological, cognitive, psychological, and social consequences of this condition.[1] The risk is relatively high in infancy: a study of over 100,000 children in Norway found that the incidence was 144 per 100,000 person-years in the first year of life, as compared to 58 per 100,000 person years for ages 1-10.[2] Current data in resource-rich countries suggests that epilepsy disproportionately affects children under three years of age compared to all other age groups.[3,4] In this age group, epilepsy differs greatly from epilepsy in older children or adults, specifically regarding etiology, clinical presentation, electroencephalographic patterns, and medical management.[3] Compared to older patients, infants with epilepsy are more likely to have neurodevelopmental comorbidities and develop medication resistant seizures.[4] Uncontrolled seizures in children 0 to 36 months old may be associated with substantial developmental, behavioral and psychological impairments. However, treatments for seizures may also cause short-term harms that can mean lower adherence or a suboptimal benefit-harm tradeoff. Thus, providers and caregivers must balance seizure control with the potential harms of epilepsy treatment.[5]

Despite the importance of managing seizures in this young population, key evidence gaps remain regarding optimal treatment. In 2015, the International League Against Epilepsy Commission of Pediatrics released a consensus document of recommendations for the management of infantile seizures.[4] The report concluded that none of the contemporary antiseizure medications (ASMs) used to treat infant epilepsy are supported by high-quality evidence.[4] Other systematic reviews on epilepsy, including a 2020 update by the National Institute for Health Care Excellence, have focused on the broader population of children, adolescents, and adults, without focusing on patients less than three years of age.[5]

For initial treatment in some epilepsies in those age 1-36 months, levetiracetam appears to the most common choice. Shellhaas et al. (2017)[6] summarized 495 children diagnosed with nonsyndromic epilepsy (i.e., not electroclinical syndrome such as West Syndrome) before 36 months of age at 17 U.S. pediatric epilepsy centers during 2013-2015. The initial choice of treatment was pharmacologic monotherapy in 94%, pharmacologic polytherapy in 3%, and no treatment in 3%. For monotherapy specifically, the chosen medication was levetiracetam in 63%, oxcarbazepine in 14%, phenobarbital in 12%, topiramate in 3%, and one of 11 other medications in the remaining 7%. However, there was wide variation in the rate of levetiracetam prescription across the 17 centers (from 29% to 75%). Further, when restricted to infants under 6 months old, levetiracetam was still the most common (55%), but phenobarbital was another common choice (31%). This variation in practice suggests the need for an up-to-date and thorough evidence review.

Nonpharmacologic strategies for seizure reduction include dietary therapies, surgical interventions, neuromodulation, and gene therapy. Dietary and surgical interventions are primarily only considered for infants with drug resistant epilepsy. Dietary therapies such as the ketogenic diet that induce metabolic changes (by increasing consumption of fat and lowering intake of carbohydrate and protein) may be particularly beneficial for infants with certain syndromes such as Dravet syndrome or Tuberous Sclerosis complex patients.[7] Potential adverse effects associated with dietary therapies include gastrointestinal symptoms, dyslipidemia,

decreased growth, and nephrolithiasis. In addition, maintaining the diet requires considerable effort from parents/families. Surgical interventions (e.g. hemispherectomy, lobectomy, focal resection) aim to reduce seizures by resection of epileptic foci, while minimizing damage to structures which could cause deficits including cognition, speech, and motor function.[8] In addition to the risk of new neurologic deficits, surgical procedures also pose peri-operative risks including bleeding, infection, hydrocephalus, and death.

Establishing seizure type, epilepsy syndrome, and etiology is critical to inform prognosis as well as guide appropriate treatment. New genetic discoveries have highlighted many varied etiologies and underscored the fact that there is no single form of infantile "epilepsy" but instead, many epilepsies. As such, even the most up-to-date seizure classification systems likely oversimplify the biological reality.[9] Genetics may play a particularly large role for epilepsies in infants age 0-36 months. In recent years, the role of genetics has been a burgeoning area of research, with the hope that epilepsy treatment can be tailored to specific genetic etiologies.[10-12]

Selecting a treatment strategy requires careful consideration of risks and benefits, particularly given uncertainties regarding efficacy and potential for adverse effects. Although uncontrolled seizures are associated with developmental delay and even death, treatments resulting in sedation or behavioral changes may also negatively impact development. These concerns are certainly echoed by parents of children with epilepsy. A 2017 survey of parents of neonates with seizures found that while over half (52%) were concerned about seizures causing brain damage, 30-33% also worried about short and long term side effects of medication.[13] These priorities appear consistent across parents considering ketogenic diet or surgery. A 2006 survey of parents of children with epilepsy about to initiate the ketogenic diet found that although seizure reduction was the top priority (69%), the second and third most important goals were reduced need for pharmacologic treatment (45%) and improved cognitive ability (35%).[14] Similarly, a 2020 survey of parents considering surgery found the primary goal was seizure freedom (98%), followed closely by reduced medication (90%), and improved cognition (82%).[15] Thus, understanding efficacy, comparative efficacy, and short and long term adverse effects of various interventions is key to inform decision-making.

To address these evidence gaps, this systematic review focused on treatment of epilepsy in children age 1 month to less than 36 months. Specifically, we addressed the comparative effectiveness of pharmacologic interventions, dietary interventions, surgical interventions, neuromodulation, and gene therapy for selected conditions. Infantile spasms were excluded from this project because of its distinctive biology, a well-defined evidence base[4,16-21] and resource constraints.

Purpose and Scope of the Systematic Review

This systematic review aimed to identify studies addressing management of epilepsies for children 1 month to less than 36 months. We assessed the effectiveness, comparative effectiveness, and harms for each intervention to support potential development of a clinical practice guideline. In addition, given the young age of the patients, caregivers play a key role in the management process. As such, we also assessed evidence on caregiver outcomes such as reduction in anxiety and quality of life.

Organization of This Report

In the remaining three chapters of this report, we describe methods for this systematic review, present results, and discuss overall findings. Within the Results chapter, we provide

results of the literature searches and screening, describe included studies, key points, detailed syntheses of the studies, and strength-of-evidence tables. The Discussion chapter reviews key findings and strength of evidence, discusses two Contextual Questions, examines the general applicability of studies, discusses implications for decision making, describes limitations of the systematic review process and the evidence base, and identifies knowledge gaps that require further research. The main body of the report is followed by Appendix A: Methods, Appendix B: Excluded Studies, Appendix C: Evidence Tables. Appendix D: Appendix References, and Appendix E: PCORI Checklist.

Methods

Review Approach

This Systematic Review follows methods outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews. We have reported the results of the systematic review in accordance with the Preferred Items for Reporting in Systematic Reviews and Meta-Analyses (PRISMA).[22] We recruited Key Informants (KIs) to refine the topic and Key Questions and provide input on the scope. We recruited a Technical Expert Panel (TEP) to provide input on all details of the protocol, including outcomes. The KIs and TEP included clinicians, researchers, surgeons, dietitians, and caregiver representatives. With feedback from the TEP, KIs, AHRQ, the National Institute of Neurological Disorders and Stroke and our partners, the American Epilepsy Society and the Patient Centered Outcomes Research Institute, we finalized the protocol and posted it on the AHRQ Effective Health Care Program's website (www.effectivehealthcare.ahrq.gov). The protocol was registered on PROSPERO (CRD42021220352). Additional methods of this review are described in Appendix A, Methods.

Key Questions

We examined evidence pertaining to three Key Questions in this review:

Key Question 1. What are the effectiveness and comparative effectiveness of pharmacologic treatments for infantile epilepsies (infants age 1 month to <36 months)?

Key Question 2. What are the effectiveness and comparative effectiveness of non-pharmacologic treatments for infantile epilepsies (e.g., dietary therapies, surgery, neuromodulation, gene therapy), including comparisons to other non-pharmacologic and/or pharmacologic therapies?

Key Question 3. What are the harms or comparative harms of treatments for infantile epilepsies?

This review also addresses two Contextual Questions:

Contextual Question 1. What are the parental preferences for treatment options for infantile epilepsies?

Contextual Question 2. What are the harms or comparative harms of not treating infantile epilepsies?

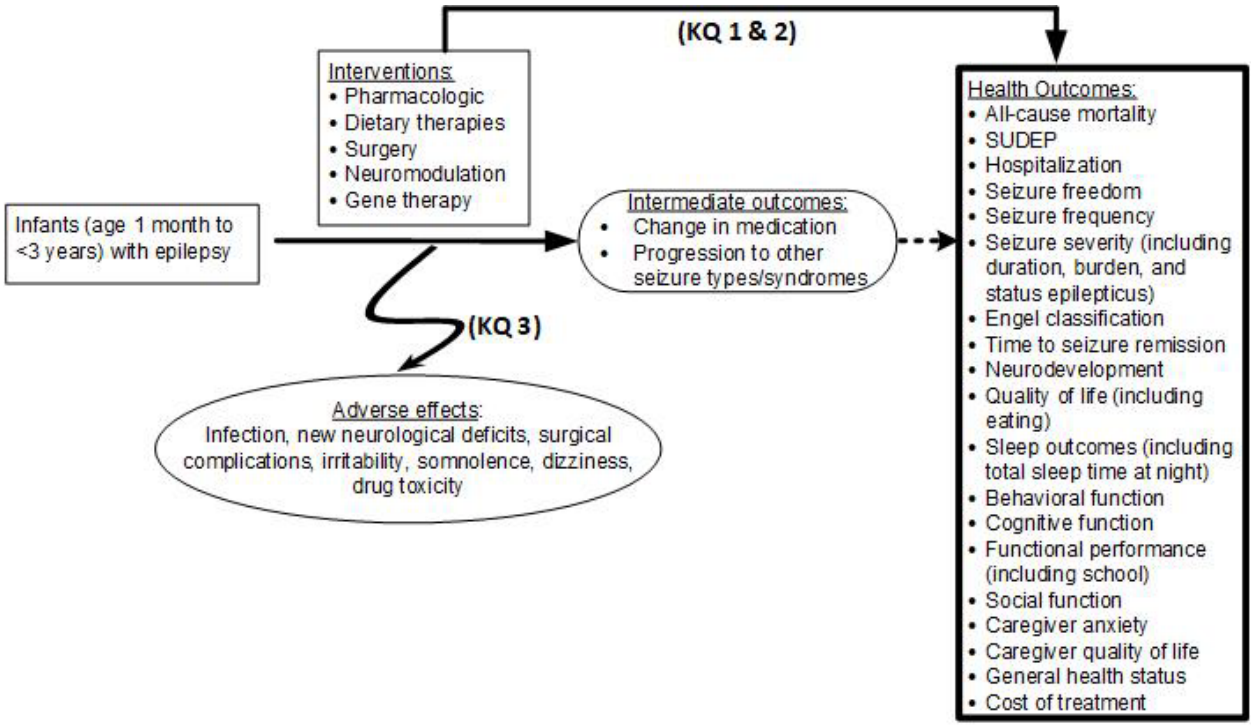
We address these two Contextual Questions in relevant results sections, referring to evidence discovered during the review process.

Analytic Framework

The analytic framework (Figure 1) visually presents the scope of this review. Infants age 1 to <36 months with epilepsy (box on the far left) receive one of five categories of interventions

(the box in the middle center). Intermediate outcomes can include medication changes or progression to other seizure types (the rounded box in the middle), and health outcomes (the box on the far right) include numerous measurements of interest. The interventions are also associated with adverse effects (the oval in the lower left).

Figure 1. Analytic framework



KQ: Key Question; SUDEP: Sudden Unexpected Death in Epilepsy

Study Selection

To identify articles relevant to each Key Question (KQ), medical librarians conducted a focused search in Embase®, MEDLINE®, PubMed®, and the Cochrane Library using a variety of terms, medical subject headings (MeSH), and major headings. (See Search Strategy in Appendix A, Methods.) The search included studies published from January 1, 1999, to August 19, 2021 and was limited to English-language and human-only studies. We also searched for gray literature in the websites of the following organizations: Centers for Disease Control and Prevention, Medscape, National Academy of Medicine, the United States Food and Drug Administration, and the sites of relevant organizations (e.g., AHRQ. We hand-searched the reference lists of relevant studies and searched for unpublished studies in ClinicalTrials.gov. The team also established a Supplemental Evidence And Data (SEAD) portal to receive additional data not found in the published literature. This portal was accessible on the AHRQ website from 2/4/2021 to 4/5/2021.

We selected studies using pre-established population, intervention, comparator, outcome, timing, and setting specifications (Table 1). For inclusion, non-randomized studies of pharmacotherapy or dietary treatment were required to have at least 30 infants per treatment, whereas for surgical treatment we only required 10 infants per procedure. Randomized trials must have included at least 10 infants per treatment. These minimums were chosen to exclude

very small studies whose results may be unrepresentative. At least 80% of patients must have been experiencing seizure types of interest (e.g., partial seizures) at the time of treatment.

We performed literature screening in duplicate using the database Distiller SR (Evidence Partners, Ottawa, Canada). Literature search results were initially screened for relevancy. We screened relevant abstracts against the inclusion criteria in duplicate, and retrieved studies in full that could meet the inclusion criteria, and we screened again in duplicate against the inclusion criteria. All disagreements were resolved by consensus discussion between two screeners. The inclusion criteria appear in the Appendix A, Methods.

Table 1. PICOTS (population, intervention, comparator, outcome, timing, setting)

Component	Inclusion	Exclusion
Population	• Infants (1 month to <36 months) diagnosed with epilepsy • Subpopulations based on baseline seizure severity/frequency, history of previous treatment, length of gestation	• West syndrome/infantile spasms • Non-epileptic seizures • Provoked seizures, including febrile seizures • Metabolic epilepsies • Status epilepticus • Acute symptomatic seizures
Intervention	• KQ 1, 3: Pharmacologic interventions (see list in Appendix A) • KQ 2, 3: Non-pharmacologic intervention: dietary therapies, surgery, neuromodulation, and gene therapy (see list in Appendix A))	• Diagnostic research • Provider/organization level interventions such as awareness campaigns • Metabolic therapies • Vitamin therapies • Social and community services
Comparator	• KQ1: Other pharmacologic interventions or usual care • KQ2: Other pharmacologic or non-pharmacologic interventions or usual care • KQ3: Inclusive of comparators for KQ 1 & 2	**n/a**

Component	Inclusion	Exclusion
Outcomes *	• All-cause mortality • SUDEP • Hospitalization • Seizure freedom • Seizure frequency • Seizure severity (including seizure duration, seizure burden, and status epilepticus) • Engel classification • Progression to other seizure types or syndromes (e.g., infantile spasms, Lennox-Gastaut Syndrome) • Time to seizure remission • Neurodevelopment • Quality of life (including eating) • Sleep outcomes (e.g., total time spent asleep at night) • Behavioral function • Cognitive function • Functional performance (including school) • Social function • Caregiver anxiety • Caregiver quality of life • General health status • Cost of treatment • Adverse events (infection, new neurological deficits, surgical complications, irritability, somnolence, dizziness, drug toxicity, etc.)	**n/a**
Timing	Effectiveness: 12-week minimum follow-up Harms: No minimum follow-up	**n/a**
Setting	Setting not limited	**n/a**

KQ: Key Question; SUDEP: Sudden Unexpected Death in Epilepsy.
*When devising our outcome list, we ensured that we captured all concepts included in the Core Outcome Set for pediatric epilepsy.[23] (There is no such set specifically for infantile epilepsies.)

Data Extraction and Risk of Bias Assessment

We extracted data from included studies into standardized forms in Microsoft Excel. We extracted all relevant study-level and patient-level characteristics (author, year, study design, country, funding source, study duration, sample size, eligibility criteria, population characteristics, clinical conditions, intervention, comparator, and results).

To assess risk of bias, we used three different instruments for different study designs. For randomized controlled trials (RCTs), we used Cochrane Risk of Bias 2;[24] for non-randomized studies with control groups, we used the Risk of Bias In Non-randomised Studies - of Interventions (ROBINS-I) instrument;[25] and for studies without control groups we used Evidence-based Practice Center guidance.[26] For the risk-of-bias items we used for each study design, see Appendix A, Methods. We rated the risk of bias of studies that reported outcomes for which we rated the strength of evidence (SOE).

Data Synthesis and Analysis

We entered all study information into tables, and where possible, we performed between-group statistical tests to determine whether outcomes favored one treatment over another. Given inter-study differences, we did not perform meta-analysis, but instead summarized data narratively. For KQ 1 (pharmacologic treatment), we discussed the evidence on each medication separately, and addressed issues of dosing within each section. For dietary treatments in KQ 2, we created two broad categories (ketogenic diet and modified Atkins diet) and discussed diet-specific issues within each section (e.g., food ratios). While other dietary interventions exist, no usable data were uncovered. For surgery in KQ 2, we categorized surgeries into three groups (hemispherectomy/hemispherotomy, non-hemispheric procedures, and tumor resection) and where possible, discussed variations within each (e.g., anatomic vs functional hemispherectomy).

Grading the Strength of the Body of Evidence

We rated the SOE using the 2013 AHRQ Methods Guide recommendations.[27] The strength of evidence was based on nine considerations: study design, risk of bias; consistency of results across trials; the directness of the evidence; effect estimate precision; reporting bias, dose-response association, magnitude of effect, and all plausible confounders would reduce the effect. Bodies of evidence consisting of RCTs were initially considered high SOE, whereas bodies of evidence consisting of non-randomized studies started at low SOE. Five domains (the first five listed above) could then potentially lower the rating, and three other domains (the last three listed above) could potentially raise the rating.

The output is a rating of the SOE: high, moderate, low, or insufficient. This rating is made separately for each outcome of each comparison of each KQ. If the evidence is sufficient to permit a conclusion, then the rating is deemed high, moderate, or low. A rating of insufficient is given if the evidence does not permit a conclusion for the outcome of interest for that KQ. Two analysts made each rating, with discrepancies resolved by consensus. We rated the SOE for the following critical outcomes: seizure freedom, seizure frequency, adverse effects, hospitalization, all-cause mortality, sudden unexpected death in epilepsy (SUDEP), quality of life, and caregiver quality of life.

Applicability

We followed the procedures outlined in the AHRQ Methods Guide to assess the applicability of the findings within and across studies.[28] We present this assessment qualitatively using the population, intervention, comparator, outcome, timing, setting) (PICOTS) framework and not a specific checklist or scale. Several *a priori* factors may limit the applicability of findings, including age, etiology, and seizure type.

Peer Review and Public Commentary

Peer reviewers with a range of expertise including epileptologists, pediatric neurosurgeons, dietitians, and other clinical care providers provided written comments on the draft report. The AHRQ Task Order Officer, an Evidence-based Practice Center Associate Editor, and representatives from the Patient Centered Outcomes Research Institute (PCORI) provided comments and editorial review. The draft report was posted for public comment on the AHRQ website. A disposition of comments report with authors' responses to the peer and public review comments will be posted after publication of the final report on the AHRQ website.

Results

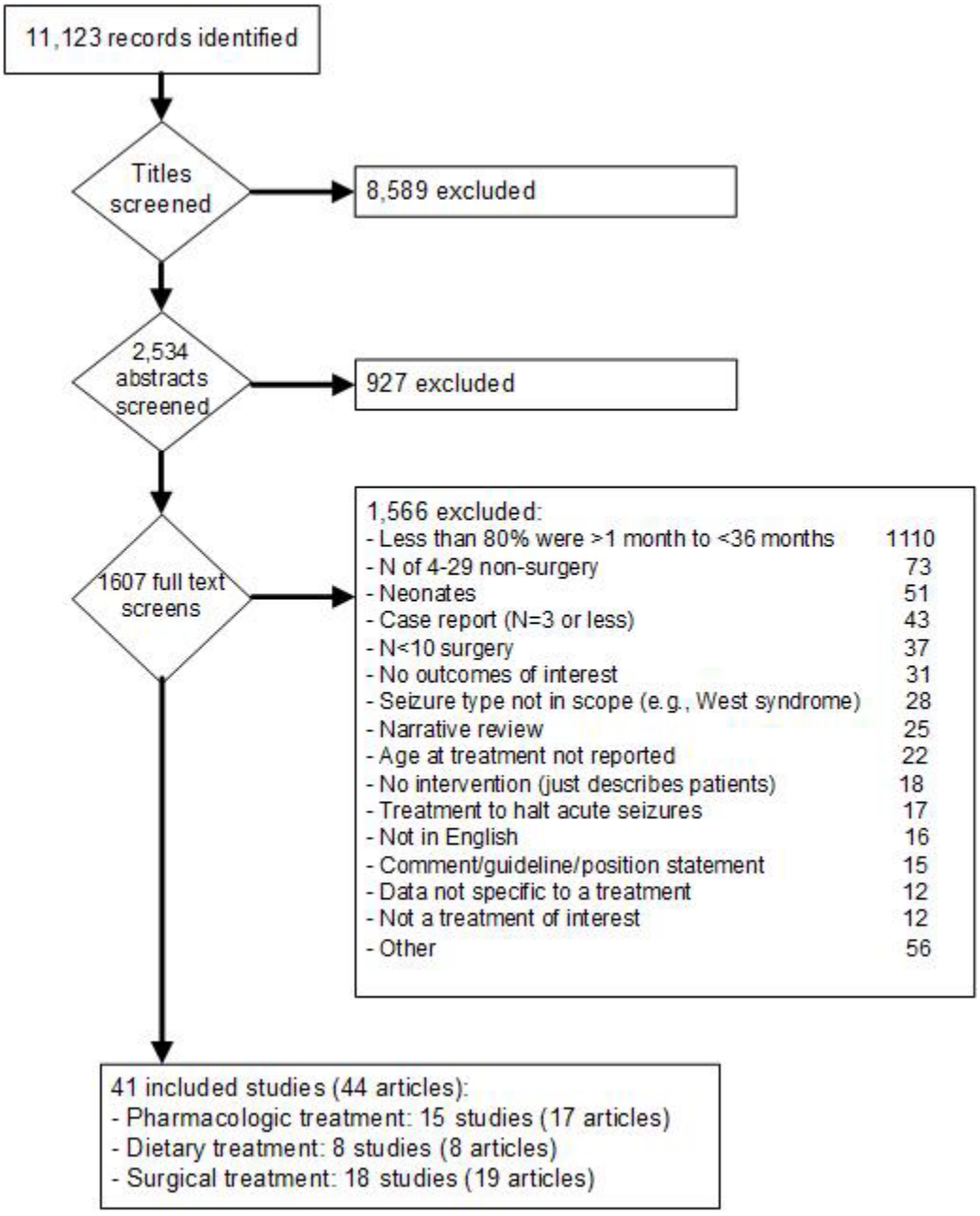
Results of Literature Searches

The electronic searches identified 11,123 citations. After title and abstract screening, 1,607 required full text review and 41 studies met our eligibility criteria for inclusion (Figure 2); see Appendix B for a list of studies excluded at full text. The most common reasons for the 1,566 full text exclusions were <80% were in the age group of interest, N of 4-29 for non-surgical interventions, and study enrolled neonates.

Only one potential dataset was submitted to the Supplementary Evidence And Data (SEAD) portal, but the data were on infantile spasms, which are outside the scope of this review.

Below we describe findings for each Key Question. Specifically, we describe included studies, list key points, and summarize treatment implementations and results.

Figure 2. Study flow diagram



Key Question 1. What are the effectiveness and comparative effectiveness of pharmacologic treatments for infantile epilepsies (infants age 1 month to <36 months)?

Description of Included Evidence

Twelve studies (published in 13 articles) met the inclusion criteria for this Key Question (Table 2). Four studies examined levetiracetam, three examined topiramate, one examined lamotrigine, one examined phenytoin, one examined vigabatrin, one example rufinamide, and one examined stiripentol. Valproate and phenobarbital were examined in separate controlled studies of levetiracetam, and we discuss their results along with levetiracetam. Carbamazepine was also examined in a non-randomized study of topiramate, and we discuss its results along with topiramate. No studies of other anti-seizure medication (ASM) met our inclusion criteria (see the full list of considered medications in Appendix A). Two studies were randomized trials, three were non-randomized comparison studies, and the other seven were pre/post studies. Four studies were conducted in the USA,[29-31] one was conducted at 27 sites in Europe,[32] and the other seven were conducted in seven different countries. The number of enrolled infants ranged from 36 to 204, and the length of follow-up ranged from 12 weeks to 2.5 years. Nine of 12 studies reported rates of seizure freedom, and these are plotted in a single figure in a dedicated section after evidence has been discussed. Appendix C provides study-specific details and enrollment criteria.

Table 2. Overview of included studies for Key Question 1

Pharmacologic Treatment	First-Line Treatment ?	Study (n)	Design	Treatment Comparison	Reported Data on Seizure Freedom?	Other Efficacy Outcome(s) Reported
Levetiracetam	Yes	Liu et al. (2020)[33] (N=100)	RCT	Valproate vs. Valproate + Levetiracetam	√	≥50%, ≥75%, cognitive ability, daily living ability, quality of life
Levetiracetam	No	Arzimanoglou et al. (2016)[32] (N=101)	Pre/Post	None	-	Epilepsy severity[b], psychomotor development
Levetiracetam	Yes	Arican et al. (2018)[34] (N=92)	Pre/Post	None	√	-
Levetiracetam	Yes	Grinspan et al. (2018)[29] (N=155)	Non-randomized comparative study	Levetiracetam vs Phenobarbital	-	Freedom from monotherapy failure[c]
Topiramate	No	Grosso et al. (2005)[35] (N=37)	Pre/Post	None	√	≥50%
Topiramate	Yes	Kim et al. (2009)[36] (N=146)	Non-randomized comparative study	Topiramate vs Carbamazepine	√	≥50%
Topiramate	No	Kholin et al. (2014)[37] (N=58)	Pre/Post	None	√	≥50%

Pharmacologic Treatment	First-Line Treatment ?	Study (n)	Design	Treatment Comparison	Reported Data on Seizure Freedom?	Other Efficacy Outcome(s) Reported
Lamotrigine	No	Piña-Garza et al. (2008)[30,38] (N=204)[a]	Withdrawal RCT and Pre/Post follow-ups	None	√	≥50%
Phenytoin	No	Sicca et al. (2000)[39] (N=55)	Pre/Post	None	√	≥50%
Vigabatrin	No	Jackson et al. (2017)[31] (N=103)	Pre/Post	None	√	≥50%, median % reduction
Rufinamide	No	Tanritanir et al. (2021)[40]	Pre/Post	None	√	≥50%, median % reduction
Stiripentol	No	Yamada et al. (2021)[41]	Pre/Post	None	-	Degree of improvement as judged by physicians

RCT = randomized controlled trials;
≥50%: the percentage of infants who had at least a 50% reduction in seizures
≥75%: the percentage of infants who had at least a 75% reduction in seizures.
[a] The RCT portion of Piña-Garza et al. (2008)[30] was only 8 weeks long, so for effectiveness data, we only included the >=12 week data reported by the open-label followup publication.[38] The RCT data were included for Key Question 3

[b] Epilepsy severity was a composite measure considering both seizure type and seizure frequency.
[c] Authors reported freedom from monotherapy failure (defined as no seizures during months 4-6 months after treatment initiation, and no second ASM other than pyridoxine was prescribed during the full six months) to improve the attribution of seizure freedom to the studied drug rather than to subsequent therapies.

Key Points

- Levetiracetam may cause seizure freedom in some infants (strength of evidence [SOE]: Low); data on quality of life are insufficient to permit conclusions (SOE: Insufficient).
- For topiramate, evidence is insufficient to permit conclusions about effectiveness, due to ancillary treatments and inconsistent results (SOE: Insufficient).
- For lamotrigine, phenytoin, vigabatrin, rufinamide, and stiripentol, evidence is insufficient to permit conclusions about effectiveness, due to the existence of only a single pre/post study for each pharmacologic treatment (SOE: Insufficient).
- Comparative effectiveness is generally unclear, but one study found the rate of freedom from monotherapy failure was higher with levetiracetam than phenobarbital.
- None of the 10 studies reported other key effectiveness outcomes such as mortality, sudden unexpected death in epilepsy (SUDEP), hospitalization, or caregiver quality of life.

Summary of Findings

We summarize the evidence separately for each ASM: levetiracetam (4 studies), topiramate (3 studies), lamotrigine (1 study), phenytoin (1 study), vigabatrin (1 study), rufinamide (1 study), and stiripentol (1 study). Valproate and phenobarbital were examined in separate controlled studies of levetiracetam, and we discuss their results in the levetiracetam section. Carbamazepine was also examined in a non-randomized study of topiramate, and we discuss its results in the topiramate section. Appendix C provides additional details about gender, race, seizure etiology,

and concomitant medications. The end of the section provides our ratings of the strength of evidence pertaining to this Key Question.

Levetiracetam

Three of the four studies measured the effectiveness of levetiracetam, while the fourth study measured the comparative effectiveness of levetiracetam and phenobarbital.

Liu et al. (2020)[33] measured the impact of levetiracetam by randomizing treatment-naïve infants to either *valproate alone* (N=50) or *valproate plus levetiracetam* (N=50). Valproate dosing was 40-50 mg/kg/day, and levetiracetam dosing was 20-30 mg/kg/day. The average age at treatment initiation was two years, but seizure types were not reported. Authors also did not report whether any patients received concomitant medications during follow-up. At 12 weeks, authors reported better results for infants receiving valproate plus levetiracetam for all eight outcomes: seizure freedom (32% vs 22%), ≥75% reduction in seizures (72% vs 50%), ≥50% reduction in seizures (96% vs 70%), quality of life (Quality of Life in Epilepsy 31 [QOLI-31] scores, mean 84 vs mean 60, scale range 0-100 where higher scores are better), daily living ability (Barthel index scores, mean 86 vs mean 62, scale range 0-100 where higher scores are better), and three cognitive ability scales (see data in Appendix C).

One concern with Liu et al. (2020)[33] is that the authors used several outcome instruments not intended for young children (the Mini-Mental State Examination, the Weschler Memory Scale-Revised in China, QOLI-31, and the Barthel instrument). We contacted the authors asking if these instruments were modified for use in young children, but received no response. However, as we drew no conclusions about these outcomes, their inclusion does not influence our main findings.

Arzimanoglou et al. (2016)[32] performed a pre/post study of 101 infants across Europe who had received levetiracetam (mean daily dose 46 mg/kg/day). The average age at treatment initiation was 6 months, 43% had focal impaired awareness seizures, 34% had focal to bilateral tonic-clinic seizures, and 25% had focal aware seizures (see other seizure types in Appendix C). At a mean of five months on levetiracetam, clinicians considered both seizure type and seizure frequency in rating each infant on a 1-7 scale where 1=marked worsening and 7=marked improvement. Improvement was marked in a third of infants (33%, 28/85), 26% (22/85) had moderate improvement, slight in 13% (11/85), and either no change or seizure worsening in the other 28% (24/85, see details in Appendix C). Clinicians also judged changes in psychomotor development using the same 1-7 scale. On this scale, improvement was marked in 19% (16/85), moderate in 13% (11/85), slight in 21% (18/85), and either no change or some worsening in the other 48% (40/85).

Arican et al. (2018)[34] performed a pre/post study of 92 treatment-naïve infants who had received levetiracetam (10-60 mg/kg/day, with 52% taking 30-40 mg/kg/day). The average age at treatment initiation was six months, 58% had focal seizures, and 42% had generalized seizures. At a median of 12 months, 66% of infants were free of seizures.

For comparative effectiveness, Grinspan et al. (2018)[29] retrospectively compared outcomes of 117 infants who received levetiracetam monotherapy to 38 infants who received phenobarbital monotherapy. The median target dose was 25 mg/kg/day for levetiracetam and 5 mg/kg/day for phenobarbital. The average age at treatment initiation was not reported, but all were under 1 year old. All had nonsyndromic epilepsy; seizure types were focal in 57%, generalized in 24%, and mixed/unclear in 19%. The only outcome reported was “freedom from monotherapy failure”, which was defined as no seizures during months 4-6 months after treatment initiation AND no

second ASM other than pyridoxine prescribed during the six months after treatment initiation. The unadjusted rates were 40% for levetiracetam (47/117) and 16% (6/38) for phenobarbital (odds ratio 3.6, 95% confidence interval [CI] 1.5 to 10, favoring levetiracetam). Due to the non-randomized design, the authors conducted numerous additional analyses to control for selection bias, and all such analyses still favored levetiracetam over phenobarbital. The authors' best estimate for the odds ratio was 4.2 (95% CI 1.1 to 16), which was based on a propensity score analysis.

Topiramate

Three studies addressed the effectiveness of topiramate, and one of the studies also addressed the comparative effectiveness of topiramate and carbamazepine.

Kim et al. (2009)[36] performed a non-randomized comparative study that enrolled treatment-naïve infants who had received either topiramate (N=41; 3 to 9 mg/kg/day) or carbamazepine (N=105; 5 to 30 mg/kg/day). The topiramate group averaged 10 months old at treatment initiation, and seizure types were generalized seizures in 71%, partial seizures in 20%, and unclassified in 10%. The carbamazepine group averaged 8.4 months old at treatment initiation, and seizure types were generalized seizures in 47%, partial seizures in 44%, and unclassified in 10%. The study did not report whether patients received concomitant medications during follow-up. Outcomes were reported an average of 30.7 months after treatment initiation. At six months, the rates of seizure freedom were 59% for topiramate and 55% for carbamazepine. The rates of ≥50% seizure reduction were 73% for topiramate and 63% for carbamazepine. Smaller reductions, no change, or aggravations occurred in 27% of those receiving topiramate and 37% of those receiving carbamazepine.

Kholin et al. (2014)[37] performed a pre/post study of topiramate that reported subgroup data on 58 infants who were age one year or younger at treatment initiation. For this subgroup, the study did not report mean age, median age, seizure types, or doses. For the overall population (N=722 including 636 who were older than 1 year), 62% were also taking additional ASM (specific medications not reported). Patients had been receiving topiramate for an average of about one year. Among 58 infants, 19% were seizure free, and 55% had ≥50% reduction in seizure frequency (timepoint not reported). The remaining 45% either had a smaller reduction, or an increase in seizures, or the appearance of new seizure types.

Grosso et al. (2005)[35] performed a pre/post study of topiramate recipients who were refractory to at least one ASM and reported subgroup data on 37 infants (median age 11 months at treatment initiation). Neither doses nor seizure types were specifically reported for these infants (although the mean dose for all 59 enrolled patients was 5.2 mg/kg/day). Specific concomitant medications were not reported for the 36 infants, but for the full population, 37% were receiving one ASM prior to starting topiramate, 41% were receiving two ASM, and 22% were receiving three ASM. At three months after starting topiramate, 8% of infants were seizure free, and 54% experienced a ≥50% reduction in seizures.

Lamotrigine

Only one included study reported effectiveness data for lamotrigine. Piña-Garza et al. (2008)[30,38] performed a withdrawal randomized trial of lamotrigine vs placebo in which all infants first received lamotrigine, and then only the lamotrigine responders (those whose seizure frequencies reduced by 40% or more) were randomized to either continue lamotrigine or receive a placebo substitution. However, as the placebo comparison period was at most eight weeks, the

randomized phase of the study did not meet our inclusion criteria for effectiveness data. Instead, for effectiveness, we included the long-term pre/post data reported by the long-term open label follow-on publication of the study.[38] In Key Question 3, we included harms data for both the randomized portion and the open label portion of the trial.

The open label study enrolled 204 infants (mean age 15.9 months at treatment initiation) with partial seizures whose seizures had not been successfully controlled on at least one ASM. Of the 204 infants, 125 infants had already participated in the randomized portion of the trial and their parents opted for continued usage of lamotrigine. The maximum lamotrigine dosage was 5.1 mg/kg/day for those on either valproate or a non-enzyme-inducing ASM, or 15.6 mg/kg/day for those on enzyme-inducing ASM. The concomitant ASM was enzyme-inducing in 59%, not enzyme-inducing in 30%, and was valproate in 11%. Seizure types were partial only in 75%, both partial and generalized in 23%, and generalized only in 1%.

At 24+ weeks' followup, 13% (26/204) of infants were seizure free, and 61% had ≥50% reduction in seizure frequency. The median seizure reduction (from a mean baseline of 21 seizures per week) was 74%.

Phenytoin

Only one included study reported effectiveness data for phenytoin. Sicca et al. (2000)[39] performed a pre/post study of 55 infants treated with oral phenytoin. Thirty-three first received phenytoin intravenously for status epilepticus and continued receiving oral phenytoin for seizure prophylaxis, whereas the other 22 infants were only treated with oral phenytoin for prophylaxis. The mean age was 7.4 months (of note, this mean represents the average for full N=82 who had received phenytoin orally only, or intravenously then orally, or intravenously only). Doses were not reported for the N=55 infants receiving oral phenytoin, but seizure types were generalized in 51% and partial in 49%. Concomitant treatments were used by 93% of infants (percentages not reported for specific medications).

At three months, the rate of seizure freedom was 4% (2/55) and the rate of ≥50% reduction in seizure frequency was 9% (5/55).

Vigabatrin

Only one included study reported effectiveness data for vigabatrin. Jackson et al. (2017)[31] reported data on 103 infants (mean age 8 months at treatment initiation) who were treated with vigabatrin (median dose 93.8 mg/kg/day at last followup which after about one year of vigabatrin treatment). Concomitant treatments included levetiracetam in 35%, topiramate in 31.1%, phenobarbital in 25.2%, and several other ASM. About 90% experienced "epileptic spasms", 15% had focal seizures, and 10% had generalized tonic seizures, and other seizure types were at most 5% prevalence among the enrolled infants.

At an average of one year on vigabatrin, 38% of infants were seizure free (33/88 with long-term followup data), 73% of infants had ≥50% reduction in seizure frequency, and the mean percentage reduction in seizures was 97% (interquartile range [IQR] 43% to 100%; baseline seizure frequency not reported).

Rufinamide

Only one included study reported effectiveness data for rufinamide. Tanritanir et al. (2021)[40] performed a pre/post study of 103 infants (median age 20 months at treatment initiation) who were treated with rufinamide (median dose was 42 mg/kg/day at last follow-up which was a

median of 15 months). Concomitant treatments included levetiracetam in 69%, topiramate in 39%, clobazam in 33%, vigabatrin in 32%, clonazepam in 20%, phenobarbital in 17%, ketogenic diet in 16%, zonisamide in 14%, valproic acid in 10%, oxcarbazepine in 7%, steroid in 7%, lacosamide in 5%, lamotrigine in 5%, and other treatments in 12%. All patients had epilepsy, and seizure types were tonic in 75%, "epileptic spasms" in 64%, myoclonic in 43%, generalized tonic-clonic in 23%, focal onset in 22%, atonic in 14%, absence in 10%, and clonic in 5%.

At a median of 15 months of treatment, 19% (20/103) were seizure-free, and 50% (51/103) had experienced at least a 50% reduction in seizure frequency. The median % reduction in seizures was 54% (from ~167/month at baseline to 90/month at followup). Twenty-three percent (24/103) had discontinued rufinamide due to a lack of efficacy.

Stiripentol

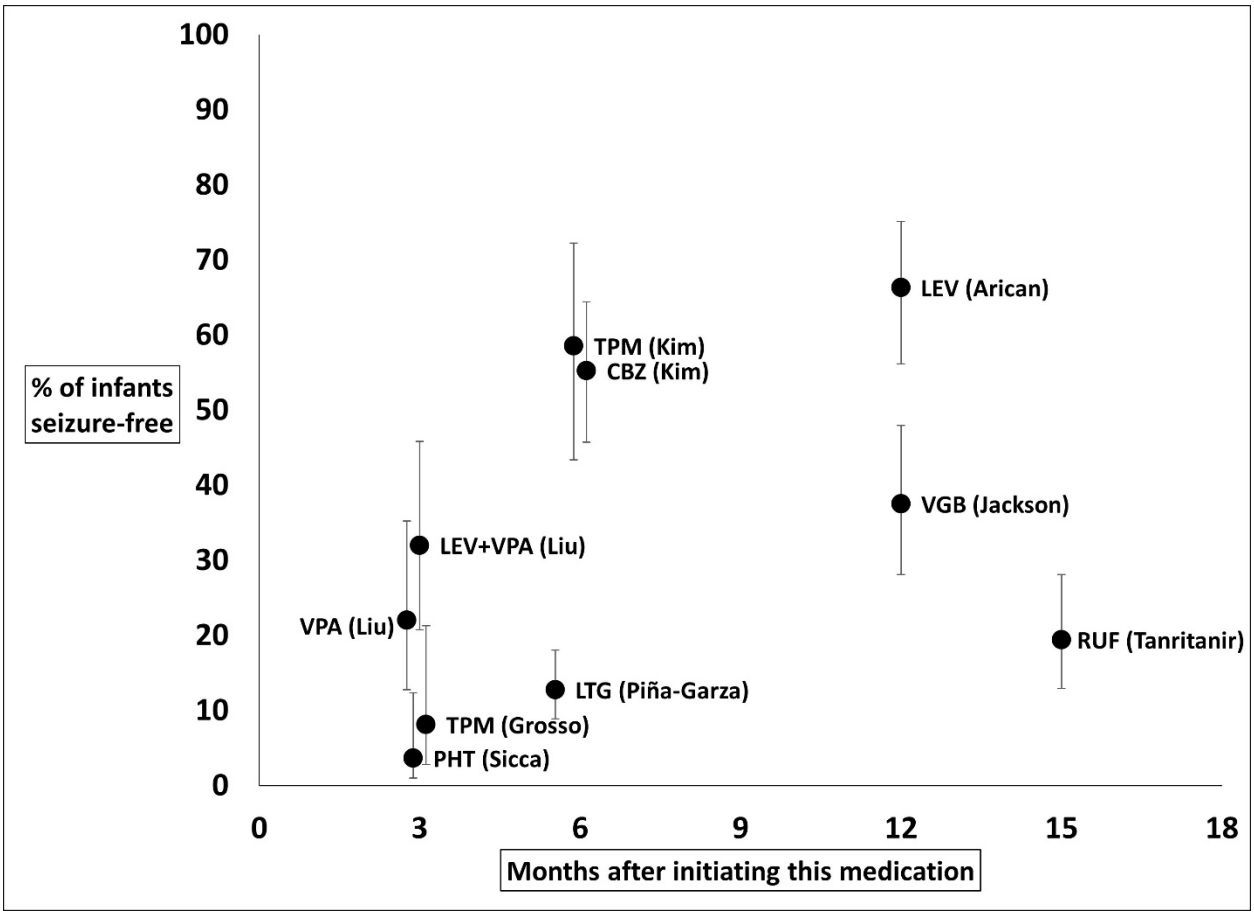
Only one included study reported effectiveness data for stiripentol. Yamada et al. (2021)[41] reported a subgroup analysis of 95 infants with Dravet Syndrome who had received stiripentol (age range 0-2 years at treatment initiation, average not reported). The dose for the 0-2 age group was not reported, but for the larger population of 376 patients, the median dose after one year was 32.5 mg/kg/day. Concomitant treatments were not reported specifically for the 0-2 subgroup, but for the full population, 99% were taking sodium valproate, 93% were taking clobazam, 41% were taking bromide, and 41% were taking topiramate. Seizure types were not reported, but all patients had Dravet Syndrome.

The only reported effectiveness outcome was the physician's judgment of the degree of improvement. Specifically, physicians rated improvement on a 1-5 scale where 1=marked, 2=moderate, 3=mild, 4=no change, 5=worsened. This was based on seizure frequency, duration, intensity, and the ability to undertake activities of daily living. At two years, 54% (50/92) were rated as having either "marked" or "moderate" improvement.

Seizure Freedom Data

Figure 3 displays the seizure freedom rates reported by eight studies at various time points (Kholin et al. (2014)[37] is not shown because the study did not report the length of follow-up). The rates ranged widely (4%-66%), and it is unclear the extent to which any specific medication caused any patient to experience seizure freedom. This may be due to many factors including the lack of control groups, concomitant medications or other factors.

Figure 3. Seizure freedom rates after initiating medications



CBZ: Carbamazepine; LTG: Lamotrigine; LEV: Levetiracetam; PHT: Phenytoin; RUF: Rufinamide; TPM: Topiramate; VGB: Vigabatrin; VPA: Valproate. The vertical bars display 95% confidence intervals. When multiple studies reported the same follow-up times, we used horizontal offsets to improve visibility. Most studies were pre/post studies, so the precise cause of seizure freedom cannot be easily determined. Studies not appearing in this figure either did not report seizure freedom rates or did not report the length of follow-up.

Strength of Evidence

Table 3 below provides our SOE) ratings for Key Question 1. The evidence that levetiracetam may cause seizure freedom in some infants is supported by one randomized controlled trial (RCT) (high risk of bias) and one pre/post study (high risk of bias). The RCT was at high risk of bias due to various concerns including unclear generation of randomization sequence, unclear concealment of allocation, possible baseline imbalance, lack of blinding of staff, and possible differential ancillary treatments. The RCT found that the likelihood of seizure freedom was 32% with levetiracetam plus valproate vs only 22% with valproate alone, and the pre/post study found a relatively high rate of seizure freedom (66%) with levetiracetam. Overall, we judged the SOE as Low that levetiracetam may cause some infants to become seizure free.

As shown in the table, we judged all other outcomes as Insufficient for other treatments. For topiramate, the reasons for insufficiency involved risk of bias (either no randomization or no control groups) as well as inconsistency (wide variation in rates of seizure freedom) and imprecision (small studies). For five other pharmacologic treatments (lamotrigine, phenytoin,

vigabatrin, rufinamide, and stiripentol, we identified only a single pre/post study of effectiveness, so we drew no conclusions. Stiripentol is not listed in the table because Yamada et al. (2021)[41] did not report any SOE-graded effectiveness outcomes.

Table 3. Strength of evidence for Key Question 1

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Levetiracetam (LEV)	Seizure freedom	One RCT[33] N=100 reported seizure freedom rates of 32% (16/50) with LEV+valproate vs 22% (11/50) with valproate alone (odds ratio 1.7, 95% CI 0.7 to 4.1) One pre/post study[34] reported 66% seizure freedom (61/92)	High	Direct	Consistent	Precise	None suspected	None	Low	Adding levetiracetam may cause seizure freedom in some infants
Levetiracetam (LEV)	Quality of life	One RCT[33] N=100 reported QOL scores of scores 84 with LEV+valproate vs 60 valproate alone (12 week follow-up) (statistically significant)	High	Direct	Unknown	Precise	None suspected	None	Insufficient	NA
Topiramate	Seizure freedom	One non-randomized comparative study[36] reported 59% seizure freedom (24/41) One pre/post study[37] reported 19% seizure freedom (11/58) One pre/post study[35] reported 8% seizure freedom (3/37)	High	Direct	Inconsistent	Imprecise	None suspected	None	Insufficient	NA
Topiramate vs carbamazepine	Seizure freedom	One non-randomized comparative study N=146:[36] topiramate 59% (24/41) vs carbamazepine 55% (58/105)	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Lamotrigine	Seizure freedom	One pre/post study[38] reported 13% seizure freedom (26/204)	High	Direct	Unknown	Precise	None suspected	None	Insufficient	NA
Phenytoin	Seizure freedom	One pre/post study[39] reported 4% seizure freedom (2/55)	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA
Vigabatrin	Seizure freedom	One pre/post study[31] reported 38% seizure freedom (33/88)	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA
Rufinamide	Seizure freedom	One pre/post study[40] reported 19%% seizure freedom (20/103)	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA
Rufinamide	Seizure frequency	One pre/post study[40] reported median 54% reduction in seizure frequency	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA

CI – Confidence interval; LEV = Levetiracetam; NA = not applicable; QOL; Quality of life; RCT – Randomized controlled trial

Key Question 2. What are the effectiveness and comparative effectiveness of non-pharmacologic treatments for infantile epilepsies (e.g., dietary therapies, surgery, neuromodulation, gene therapy), including comparisons to other non-pharmacologic and/or pharmacologic therapies?

Description of Included Evidence

We included 24 studies for this Key Question, including 8 of dietary interventions and 16 studies of surgical interventions published in 17 articles; see Table 4. Only two were RCTs, both assessing dietary interventions. The remaining 22 studies were pre/post studies. Many surgical studies described outcomes for more than one surgical procedure used for different patients. Because indications for selecting a specific surgical procedure are typically so specific to individual patients (i.e., the location, size and distribution of seizures), we did not categorize these as comparative studies, but considered each one to be a pre/post study of multiple procedures. No studies assessed neuromodulation or gene therapy.

Appendix C provides study characteristics, treatment details, patient characteristics, risk of bias, and results. In the first half of this section, we describe dietary interventions; in the second half, we describe surgical interventions.

Table 4. Overview of included studies for Key Question 2

Treatment	Study	Design	Treatment Comparison(s)
Ketogenic Diet	El-Rashidy et al. 2013[42] (N=40) Kim et al. 2015[43] (N=57)	RCT	Modified Atkins diet, No dietary change Modified Atkins diet
Ketogenic Diet	Suo et al. 2012[44] (N=147) Wu et al. 2015[45] (N=40) Kim et al. 2019[46] (N=49) Dressler et al. 2015[47] (N=58) Kang et al. 2005[48] (N=49) Liu et al. 2021[49] (N=41)	Pre/post	NA
Hemispherectomy/hemispherotomy	Otsuki et al. 2013[50] (N=18) Reinholdson et al. 2015[51] (N=12) Kadish et al. 2019[52] (N=22) Steinbok et al. 2009[53] (N=48) Kumar et al. 2015[54] (N=16) Iwasaki et al. 2015[55] (N=10) Schramm et al. 2012[56] (N=21) Pinto et al. 2014[57] (N=15) Cook et al. 2004[58] (N=55) Jonas et al. 2004[59] (reports on subgroup of Cook et al. 2004[58]) Lettori et al. 2007[60] (N=10) Loddenkemper et al. 2007[61] (N=14) Roth et al. 2021[62] (N=48)	Pre/post	NA
Other resective surgery	Reinholdson et al. 2015[51] (N=24) Kadish et al. 2019[52] (N=26)	Pre/post	NA

Treatment	Study	Design	Treatment Comparison(s)
	Loddenkemper et al. 2007[61] (N=10) Steinbok et al. 2009[53] (N=58) Sugimoto et al. 1999[63] (N=10) Kalbhenn et al. 2019[64] (N=10) Maton et al. 2007[65] (N=13) Roth et al. 2021[62] (N=19)		
Brain tumor resection	Gaggero et al. 2009[66] (N=20)	Pre/post	NA

RCT = Randomized controlled trial
NA = Not applicable

Description of Included Evidence for Dietary Interventions

Eight studies assessed effectiveness of the ketogenic diet (KD) intervention (Table 5). Two RCTs compared KD to the modified Atkins diet (MAD). In addition, one of the RCTs also included a control group (no dietary intervention). The remaining six studies were pre/post studies (three retrospective, three prospective) assessing KD (one[49] enrolled a group of normal infants without seizures, and since this group is not relevant to this report, we considered it a pre/post study for our purposes). No other dietary interventions met the inclusion criteria.

Table 5. Summary of dietary interventions

Study (Country)	Treatments	Description of Treatment	Follow-Up Duration	Reported Data on Seizure Freedom?	Reported Data on Seizure Frequency?
Suo et al. 2012[44] (China)	Ketogenic Diet	Johns Hopkins Protocol	12 months	√	√
Wu et al. 2015[45] (China)	Ketogenic Diet	Johns Hopkins Protocol	6 months	√	√
Kim et al. 2019[46] (US)	Ketogenic Diet	Range of 3:1, 3.5:1, and 4:1 lipid to non-lipid ratio.	3 months	-	√
Dressler et al. 2015[47] (Austria)	Ketogenic Diet	Johns Hopkins Protocol	18 months	√	√
Kang et al. 2005[48] (Korea)	Ketogenic Diet	Johns Hopkins Protocol	12 months	√	√
Liu et al. 2021[49] (China)	Ketogenic Diet	Classic (unspecified)	12 months	-	√
El-Rashidy et al. 2013[42] (Egypt)	• Ketogenic Diet • Modified Atkins Diet • Control	• Classic 4:1 lipid to nonlipid ratio with ASM polytherapy • 60% fat, 30% protein, and 10% carbohydrates by weight with ASM polytherapy	> 6 months	-	√

Study (Country)	Treatments	Description of Treatment	Follow-Up Duration	Reported Data on Seizure Freedom?	Reported Data on Seizure Frequency?
		• ASM polytherapy with no dietary changes			
Kim et al. 2015[43] (Korea)	• Ketogenic Diet • Modified Atkins Diet	• 4:1 lipid to nonlipid ratio and nonfasting initiation protocol • Johns Hopkins Protocol	6 months	√	√

ASM -Antiseizure medication(s)

Key Points: Dietary Interventions

- The ketogenic diet may cause seizure freedom in some infants, and may reduce average seizure frequency (SOE: Low).
- The modified Atkins diet may reduce the frequency of seizures (SOE: Low), but evidence on seizure freedom was insufficient to permit conclusions (SOE: Insufficient).
- The ketogenic diet may cause greater reductions in seizure frequency than the modified Atkins diet (SOE: Low), but data on seizure freedom are inconclusive (SOE: Insufficient).

Summary of Findings: Dietary Interventions

Ketogenic Diet

Two RCTs assessed the effectiveness of KD and MAD. In the first RCT, El-Rashidy et al. (2013)[42] conducted a three-arm RCT comparing KD and MAD to a control group (no-dietary-change). All enrolled patients were under 36 months of age (n=40). The KD intervention was described as the classic 4:1 KD, administered via a liquid formula (Ketocal 4:1 milk from Danone, Nutricia). In addition to the dietary intervention, all maintained the same doses of ASM (valproic acid, carbamazepine and/or clonazepam) throughout the study period.

In the second RCT, Kim et al. (2015)[43] randomized patients to KD or MAD (see a discussion of the between-group comparison in the next section on KD vs MAD). Although the study enrolled patients ages 1 to 18 years, authors provided a subgroup of patients 1 to <2 years of age. The KD interventions followed the 4:1 lipid to nonlipid ratio with a nonfasting initiation protocol. While the MAD adhered to the Johns Hopkins protocol, the authors did not report if the KD used conformed to the protocol.

In the first pre/post study, Suo et al. (2012)[44] prospectively enrolled 317 consecutive patients with intractable epilepsy to receive KD, of whom 147 patients were 0-2 years old and met criteria for inclusion. Infants received the Johns Hopkins Hospital protocol, with a lipid-to-non-lipid ratio of 4:1. However, there was variation in how the diet was initiated across the study. Depending on the date of KD initiation, the patient's diet may have been self-prepared via the KD Meal Planner, KetoCal ketogenic formula, or a KD Meal Planner supplemented by various liquid milk, cookies, and set meals. Follow-ups were conducted either at an outpatient clinic or by phone call.

Wu et al. (2015)[45] conducted a prospective pre/post study of KD in 87 children diagnosed with drug-resistant epilepsy. The authors did not clarify whether enrollment was selective or consecutive. The intervention used the Johns Hopkins protocol, with the addition of 24 to 48

hours pre-diet fast in the hospital. Of the 87 children in the study, only 40 (46%) met our inclusion criteria of under 36 months of age. Of the 40 infants, six were between the ages of 0 to 1 year, and 36 were between the ages of 1 to 3 years (36 months).

Kim et al. (2019)[46] presented a retrospective chart review of patients with medically intractable epilepsy who started the KD. The KD protocol was determined internally with a multidisciplinary team, and was not described as being based on specific established protocols. KD was initiated at a 1:1 fat to carbohydrate + protein ratio and steadily increased to 3:1, but not all patients maintained on the 3:1 ratio. Twenty patients maintained the 3:1 ratio, 13 progressed to 3.5:1, while 59 were on 4:1 ratios or higher. Roughly one-third of patients were on solid food, liquid food, or both solid and liquid foods each. All patients were under 3 years of age, and we only extracted data on the subgroup of patients without West syndrome.

Dressler et al. (2015)[47] evaluated the seizure relapse rate with a retrospective chart review of children treated with KD between March 1999 to April 2014. The intervention followed the Johns Hopkins protocol, without an initial fasting period. Of the 115 patients with complete clinical and follow-up data, 58 (50.4%) were under 1.5 years of age at the start of the KD. The outcomes the authors reported specifically for this subgroup were seizure freedom and "responders", defined as a reduction in seizure frequency of ≥ 50%. Multiple durations of KD were also reported (3, 6, 12 months) and an additional 6 months after the KD ended.

Kang et al. (2005)[48] performed a retrospective review of young patients with uncontrolled epilepsy treated with KD. The protocol used was the Johns Hopkins protocol, but not all patients had initial fasting and fluid restriction. Of the 199 patients enrolled in the study, 49 (24.6%) were < 2 years old. Follow-up was conducted up to 12 months.

Liu et al. (2021)[49] enrolled 41 infants diagnosed with refractory epilepsy unresponsive to two or more anticonvulsants. Although the study's primary goal was to examine biological and biochemical effects of the KD on infants, it did report seizure frequencies for infants treated with KD. Study authors did not specify what dietary protocol was used and some infants received different KD protocols. Infants in the KD group were further stratified into various age groups, but each individual subgroup contained too few patients to be analyzed independently according to protocol. All patients were followed for 12 months.

Seizure Freedom

Five studies (1 RCT, 4 pre/post studies) assessing KD reported the proportion of infants achieving seizure freedom. No studies reporting on seizure freedom compared KD to a control.

One RCT (Kim et al. 2015),[43] compared outcomes for infants receiving KD or MAD. For KD, at both 3 and 6 months, 53% (9/17) of infants were seizure-free. (It was unclear if the same nine patients were seizure free at both time points). More discussion about the direct comparison of KD and MAD is presented in a later section.

Seizure freedom rates across the four pre/post studies ranged from 11.6% to 53%. Suo et al. (2012)[44] reported seizure freedom rate of 11.6% (17/147). Notably, the study had high treatment attrition: only 33 of 147 children remained on the diet and reported on seizure freedom. Wu et al. (2015)[45] reported seizure freedom rates of 25% (10/40) at 2 months, and 33% (13/40) at six months.

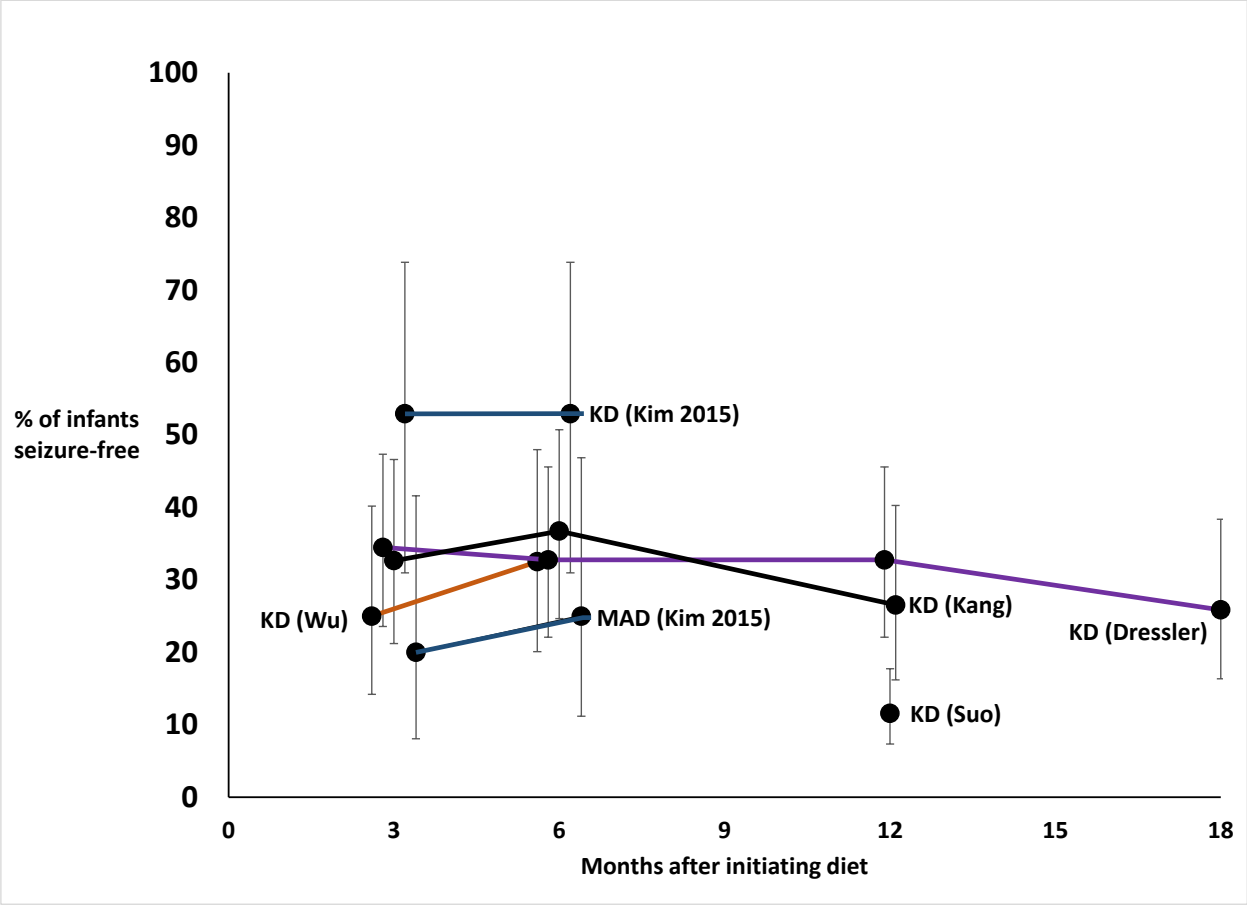
Dressler et al. (2015)[47] was not clear and consistent in its outcome reporting for this subgroup, with ambiguous information presented in the text of the article and some conflicting information between the text and the figures. The article reported 20 of 58 patients (34%) seizure free three months into the KD. At both six months and 12 months, 19 of 58 patients (33%) were

seizure free. The author also reported that 15 of 58 patients (26%) were seizure free six months after the cessation of the KD.

Kang et al. (2005)[48] reported 16 of 49 patients (32%) seizure free at three months, 18 of 49 patients (36%) seizure free at six months, and 13 of 49 patients (26%) seizure free at 12 months. It is unclear at each timepoint how many patients were still on the KD, and the denominator of 49 patients represents the total number of patients that had initiated the diet. At 12 months follow-up, only 13 of the original 49 patients (27%) in the < 2 years subgroup were still receiving the KD.

Figure 4 shows the seizure freedom proportion experienced at various time points for the five studies included here. Kim et al. (2015)[43] reported data for both KD and MAD, which are each displayed in the figure. Seizure freedom rates for KD ranged from 25%-53%.

Figure 4. Seizure freedom rates after initiating dietary interventions



KD – Ketogenic diet; MAD – Modified Atkins Diet. The vertical bars display 95% confidence intervals. When multiple studies reported the same follow-up times, we used horizontal offsets to improve visibility. For Dressler et al., the data shown at 18 months represent seizure freedom rate for 6 months after the 12 months KD intervention. Only one study, Kim 2015, had seizure freedom data for MAD. All other studies shown were pre/post studies, so the precise cause of seizure freedom cannot be easily determined. Studies not appearing in this figure either did not report seizure freedom rates or did not report the length of follow-up.

Seizure Frequency

All eight studies reported seizure frequency outcomes.

In the RCT with three arms (KD, MAD, and regular diet), El-Rashidy et al. (2013)[42] reported that the KD group had 58% reduction in seizures at three months (compared to a 6% increase for the normal diet group) and had 71% reduction in seizures at six months (compared to an 8% reduction for the normal diet group). For seizure severity as measured by Chalfont scores, the KD group had 32% improvement at three months (compared to only 0.45% improvement for the normal diet group), and had 36% reduction in seizures at six months (compared to only 2% improvement for the normal diet group). All of these comparisons were statistically significant (favoring KD over regular diet).

In Kim et al. (2015),[43] the authors reported of the 17 patients on KD, nine experienced >90% reduction, and ten experienced >50% reduction at three months. The mean reduction in frequency was 19% of the baseline seizure frequency (i.e., a mean reduction of 79% from baseline). At six months, ten patients experienced >90% reduction, and ten patients experienced >50% reduction.

Suo et al. (2012)[44] reported reduction in seizure frequency after 12 months on the diet for children age 1 to <2 years. Of the 147 children in this age group, only 33 patients remained on the diet. Of these 33 patients, 17 were seizure free, 3 experienced 90% to 99% seizure frequency reduction, 7 experienced 50% to 90% reduction, and 6 had either less than 50% reduction or no reduction.

Wu et al. (2015)[45] reported both reduction of seizure frequency after 6 months on the KD and efficacy of KD after three months. Efficacy was defined as experiencing >90% seizure reduction. After three months on the KD, the authors reported the KD effective in 13 of 40(32.5%) children under 36 months. At six months, two of 40 patients experienced >90% reduction (not counting seizure free patients), with an additional six patients experiencing 50% to 90% seizure reduction. While the article mentioned measurement of baseline seizure frequencies, baselines were not reported.

Kim et al. (2019)[46] reported the response of KD, defined as experiencing a seizure reduction >50%. We only extracted data from those without West syndromes. The authors reported that 18 of 49 patients (36%) responded to KD.

Dressler et al. (2015)[47] was not clear and consistent in its outcome reporting for this subgroup, with ambiguous information presented in the text of the article and some conflicting information between the text and the figures. The only outcome reported for the infants was a response to KD. Response to the diet is defined as "the absolute reduction in seizure frequency of ≥50% at follow-up, compared to baseline". The article reported 37 (63.8%) responded to KD 3 months into the diet. At 6 months into the KD, 32 (55.2%) responded to the diet. At 12 months, 27 (84.3%) responded to KD. At 6 months after the diet ended, 21 (42.9%) were responders. The study was unclear regarding the how many patients were on the diet at those timepoints, and the percentages they reported were inconsistent.

Kang et al. (2005)[48] reported rates of >50% reduction of 56% at three months (28/49), 54% at six months (27/49), and 32% at 12 months (16/49). For each time point, the authors also recorded how many patients continued the diet, but it was not clear whether that was measuring how many patients were still on the KD at the time of outcome measurement or after measuring the outcome decided to continue the diet further. Nevertheless, by 12 months only 13 of the original 49 patients (27%) in the subgroup continued the diet.

Liu et al. (2021)[49] reported that >=50% seizure reduction occurred in 28 (68%), 32 (78%), and 34 (83%) of patients at 3, 6, and 12 months, respectively. They also reported that 7 (17%), 8 (20%), and 9 (22%) experienced >=90% seizure reduction at 3, 6, and 12 months, respectively.

Modified Atkins Diet

The Modified Atkins Diet (MAD) is a less restrictive dietary alternative to the ketogenic diet, with a focus on low carbohydrate intake but no restrictions on proteins, dairy, or fat. Two RCTs assessed the MAD. However, only one study, El-Rashidy et al. (2013)[42] compared MAD to a control group (ASM polytherapy arm). The MAD demonstrated statistically significant reduction in seizure frequency compared to control at 6 months, but not at three months. Specifically, at six months, seizure reduction was 28% (MAD) compared to 8% (control), $p<0.001$. Compared to control, the MAD also demonstrated a statistically significant improvement in seizure severity (measured as Chalfont score) at both three and six months.

Ketogenic Diet Versus Other Diets

Two studies directly compared the KD with the MAD. El-Rashidy et al. (2013)[42] reported that KD yielded significantly greater reduced seizure frequency at three and six months compared to the MAD. Specifically, at six months, seizure reduction was 71% (KD) vs. 28% (MAD), <0.001. However, there was no statistically difference in seizure severity (measured by Chalfont score).

Kim et al. (2015)[43] reported KD demonstrated a statistically significantly higher rates of seizure freedom compared to MAD, with 9 of 17 achieving seizure freedom for KD and 4 of 40 for MAD at three months. This difference was not sustained; at six months the two groups demonstrated statistically non-significant difference. All other outcomes (i.e., >90% and >50% seizure reduction) also demonstrated no statistically significant difference between groups. The authors did find that at six months, the KD yielded lower mean and median percentage of baseline seizures than the MAD.

Strength of Evidence: Dietary Interventions

Table 6 provides SOE ratings dietary interventions. The evidence was sufficient to permit conclusions that the KD may cause seizure freedom in some infants (SOE: Low) and that seizure frequencies are generally lower after starting the KD (SOE: Low). For comparative effectiveness, two randomized trials support the conclusion that seizure frequencies are lower after the KD than the MAD. Due to the marked differences in protocol, design, and patient population between the studies, we deemed meta-analysis inappropriate.

Table 6. Strength of evidence for Key Question 2: Dietary interventions

Treatment	Outcome	Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Ketogenic Diet	Seizure freedom	One RCT[43] compared KD with MAD reported 9 of 17 (53%) patients were seizure free at both time points. <u>3 months</u>: Three pre/post studies[45,47,48] reported seizure freedom rates of 25% 34.5% and 32.7% <u>6 months</u>: Three pre/post studies[45,47,48] reported seizure freedom rates of 32.5%, 32.8%, and 36.7% <u>12 months</u>: Three pre/post studies[44,47,48] reported seizure freedom rates of 11.6%, 32.8%, and 26.5% <u>6 months After KD:</u> One pre/post[47] study reported 25.9%.	High	Direct	Consistent Although seizure freedom rates were inconsistent, all studies report some seizure freedom	Precise	None suspected	All studies are patients with intractable epilepsy	Low	Ketogenic diet may cause seizure freedom in some infants
Ketogenic diet	Seizure frequency	One RCT[42] reported KD statistically significantly reduced seizure frequency by 57.95±17.73 compared to control at 3 months and by 70.79±19.26 at 6 months.	High	Direct	Consistent	Imprecise	None suspected	All patients have intractable epilepsy	Low	Ketogenic diet may reduce seizure frequency

Treatment	Outcome	Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
		<u>3 months:</u> One RCT[43] and five pre/post studies[45-49] Rates of ≥90% reduction (3 studies) were 53%, 17%, and 8% Rates of ≥50% reduction (5 studies) were 68%, 64%, 59%, 57%, and 37% <u>6 months:</u> One RCT[43] and four pre/post studies[45,47-49] Rates of ≥90% reduction (3 studies) were 59%, 18%, and 5% Rates of ≥50% reduction (4 studies) were 78%, 59%, 55%, and 55% <u>12 months:</u> Four pre/post[44,47-49] Rates of ≥90% reduction (2 studies) were 22% and 2% Rates of ≥50% reduction (3 studies) were 85%, 83%, and 33% <u>6 months after KD:</u> One pre/post[47] reported that 43%) experienced ≥50% reduction								

Treatment	Outcome	Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Modified Atkins Diet	Seizure freedom	One RCT[43] reported 4 of 20 patients seizure free at 3 months and 5 of 20 patients seizure free at 6 months.	High	Direct	Unknown	Precise	None suspected	None	Insufficient	NA
Modified Atkins Diet	Seizure frequency	One RCT[42] found that compared to control (n=10), MAD (n=15) reduced seizure frequency (**28**% vs. 8%, MAD and control, respectively) at 6 months. One RCT[43] reported the MAD (n=20) reduces the seizure frequency by 46.18% at 3 months and 39.76% at 6 months compared to baseline.	High	Direct	Consistent	Precise	None suspected	None	Low	MAD may reduce seizure frequency.
Ketogenic diet vs. Modified Atkins diet	Seizure freedom	One RCT[43] (n=37) found that compared to MAD, patients receiving KD had higher rates of seizure freedom at 3 months: 53% vs. 20%, (odds ratio 4.05, 95% CI 1.05 to 20). However, this difference was not statistically significant at 6 months (53% vs 25%, odds ratio 3.4, 95% CI 0.84 to 13.5).	High	Direct	Unknown	Precise	None suspected	None	Insufficient	NA
Ketogenic diet vs. Modified Atkins diet	Seizure frequency	One RCT[42] (n=40) found KD was more effective at reducing the seizure frequency than	High	Direct	Consistent	Precise	None suspected	None	Low	KD reduces seizure frequency

Treatment	Outcome	Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
		MAD at both 3 and 6 months. One RCT[43] reported results in the same direction (favoring KD over MAD) but results were not statistically significant.								more than MAD

CI = Confidence interval; KD = Ketogenic diet; MAD = Modified Atkins Diet; NA = not applicable; RCT = randomized controlled trial

Description of Included Evidence for Surgery

Sixteen studies (published in 17 articles) were included for effectiveness data on surgical interventions for infants with epilepsy undergoing surgery at 1 to <36 months. We included all studies describing outcomes for a procedure of interest for ≥ 10 infants. Table 7 provides an overview of included studies, number of infants, years operations were performed, and key outcomes. Surgical interventions may be resective (hemispherectomy/hemispherotomy, nonhemispheric procedures) or palliative (e.g., corpus callosotomy, multiple subpial transections) or involve neuromodulation. No included studies assessed palliative procedures or neuromodulation.

We identified studies of infants receiving hemispherectomy/hemispherotomy (12 studies, reported in 13 articles), other non-hemispheric resections (8 studies), tumor resection only (1 study). All included studies were retrospective pre/post studies which obtained data from chart reviews (16 studies) or registry data[51] (1 study).

Five studies were conducted in the U.S. The remaining 11 non-US studies were conducted in Germany[52,56,64] (n=3), Japan[50,55] (n=2), Canada[53,63] (n=2), Italy[60,66] (n=2), Sweden[51] (n=1) or included data from multiple countries (n=1).[62] All US studies were single center studies from University of California at Los Angeles,[58,59] University of Colorado,[54] Cleveland Clinic,[61] Boston Children's hospital,[57] and Miami Children's hospital.[65] One study (Roth et al.[62]) included data from 19 centers with surgical procedures performed from 1999 to 2020. Data from 6 patients cared for at 2 of 19 centers (University of California at Los Angeles and Cleveland Clinic) may also have been included in other studies[58,59,61] given overlap in time periods (Figure 5 and author correspondence).

As nearly all data represent either subgroups or individual patient data, patient characteristics such as age, seizure etiology, and length of follow-up were variably reported. No studies reported on race. The number of infants meeting inclusion criteria from each study ranged from 10 to 58. Appendix C provides detailed information regarding inclusion criteria, patient characteristics, treatments, and outcomes.

Risk of bias (ROB) ratings for all studies are also provided in Appendix C. As all studies assessing surgical interventions were pre/post studies lacking a control group and retrospective, the overall ROB for all studies was high.

Table 7. Overview of surgical studies

Treatment	Study	Years Procedures Performed	Procedure(s)	N	Reported Data on Seizure Freedom?[a]	Reported Data on Seizure Frequency?
Hemispherectomy/ hemispherotomy	Cook et al. 2004[58] Jonas et al. 2004[59b]	1986 - 2002	Anatomical hemispherectomy (n=14) Functional hemispherectomy (n=15) Hemispherotomy (n=26)	55	√	-
Hemispherectomy/ hemispherotomy	Iwasaki et al. 2015[55]	2001 - 2012	Hemispherotomy	10	-	√
Hemispherectomy/ hemispherotomy	Kadish et al. 2019[52]	2001-2014	Hemispherotomy	22		√
Hemispherectomy/ hemispherotomy	Kumar et al. 2015[54]	2002 - 2013	Hemispherotomy	16	-	√

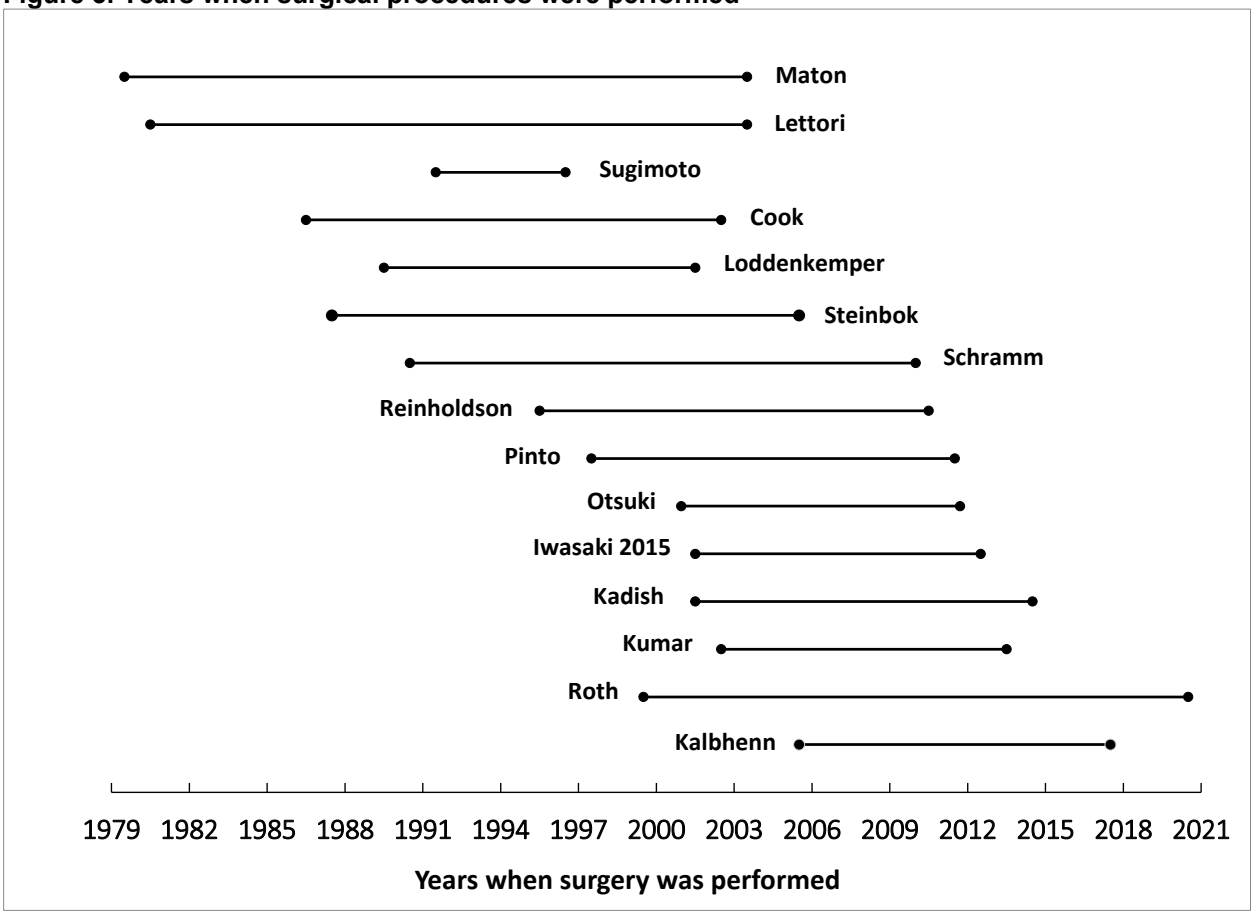
Treatment	Study	Years Procedures Performed	Procedure(s)	N	Reported Data on Seizure Freedom?[a]	Reported Data on Seizure Frequency?
Hemispherectomy/ hemispherotomy	Lettori et al. 2007[60]	1980 - December 2003	Functional Hemispherectomy/Hemispherotomy	10	√	√
Hemispherectomy/ hemispherotomy	Loddenkemper et al. 2007[61]	1989 - 2001	Hemispherectomy	14	√	√
Hemispherectomy/ hemispherotomy	Otsuki et al. 2013[50]	December 2000 to August 2011	Hemispherotomy	18	√	√
Hemispherectomy/ hemispherotomy	Pinto et al. 2014[57]	1997 - 2011	Anatomic hemispherectomy, Functional hemispherectomy, and Peri-insular hemispherotomy	15	√	√
Hemispherectomy/ hemispherotomy	Reinholdson et al. 2015[51]	1995 - 2010	Hemispherotomy	12	√	√
Hemispherectomy/ hemispherotomy	Roth et al. 2021[62d]	1999 – 2020	Periinsular, vertical functional hemispherotomies, anatomic hemispherectomy[e]	48	√	√
Hemispherectomy/ hemispherotomy	Schramm et al. 2012[56]	1990 through end of 2009	Hemispherotomy	21	√	-
Hemispherectomy/ hemispherotomy	Steinbok et al. 2009[53]	January 1987 to September 2005	Anatomic hemispherectomy, hemidecortication, functional hemispherotomies, periinsular hemispherotomies	48	-	√
Other resective surgery	Kadish et al. 2019[52]	2001-2014	Intra or multilobar resection	26		√[c]
Other resective surgery	Kalbhenn et al. 2019[64]	2005 - 2017	Posterior disconnection	10	√	-
Other resective surgery	Loddenkemper et al. 2007[61]	1989 - 2001	Focal cortical resection	10	√	√
Other resective surgery	Maton et al. 2007[65]	1979 - 2003	Temporal lobe resection	13	-	√
Other resective surgery	Reinholdson et al. 2015[51]	1995 - 2010	Temporal or Frontal lobe resection	24	√	√
Other resective surgery	Roth et al. 2021[62]	1999 - 2020	Focal resection, Lobectomy	19	√	√
Other resective surgery	Steinbok et al. 2009[53]	January 1987 to September 2005	Lesionectomy or Cortical Resection	58	-	√

Treatment	Study	Years Procedures Performed	Procedure(s)	N	Reported Data on Seizure Freedom?[a]	Reported Data on Seizure Frequency?
Other resective surgery	Sugimoto et al. 1999[63]	1991 to 1996	Focal cortical resection	10	√	√
Brain Tumor Resection	Gaggero et al. 2009[66]	"A 10 year period"	Supratentoral tumor resection	20	-	√

[a] Study reported Engel Outcome IA or ILAE I; in cases, where studies did not report Engel or ILAE outcomes, but described seizure freedom, we included these outcomes as well.
[b] Jonas et al. reports on a subset of 16 patients with hemimegalencephaly (HME) contained in Cook et al.
[c]For Kadish et al. seizure frequency for other resections represented outcomes for 17 intralobar resections which were the final surgery.
[d] Roth et al. included data from 19 centers. Data from 6 patients cared for at 2 of 19 centers was also potentially reported in other studies[58,59,61]providing seizure outcome data with some overlap in time period of procedures. Thus, it is possible that Roth et al. included data from 6 patients already captured in other studies.
[e]The 48 hemispheric procedures described included 1 "unknown" type of hemispheric procedure.
Gaggero et al. describes seizure freedom as Engel I; however, as we required studies to report Engel Ia for the outcome of seizure freedom, this data was not included here.

Studies included surgeries performed over a broad range of years (Figure 5).

Figure 5. Years when surgical procedures were performed



Note: Studies not appearing in this figure either were not included for effectiveness data, or did not report the years when surgery was performed.

Key Points: Surgery

- **Hemispherectomy/hemispherotomy**: Some infants with medically refractory epilepsy achieve seizure freedom after hemispherectomy/hemispherotomy (8 retrospective pre/post studies, SOE: Low).
- **Hemispherectomy/hemispherotomy**: Over half of infants achieved a favorable outcome (Engel I or II, ILAE I to IV, or >50% seizure reduction) at follow-up of >1 year. However, evidence is insufficient to draw a conclusion due to study limitations (9 retrospective pre/post studies, SOE: Insufficient).
- **Other resections**: Some infants with medically refractory epilepsy achieve seizure freedom after intralobar, multilobar, focal cortical resection, or posterior disconnection surgery (5 retrospective pre/post studies, SOE Low).
- **Other resections**: All studies reported that at least 50% of infants undergoing resection (intra/multilobar/focal cortical resection or posterior disconnection) achieved a favorable outcome (Engel I or II, ILAE I to IV, or >50% seizure reduction). However, due to study limitations, evidence is insufficient to draw a conclusion (6 retrospective pre/post studies, SOE: Insufficient).

- **All surgical interventions**: No studies described quality of life for children or caregivers, or treatment cost (SOE: Insufficient).
- **All surgical interventions**: Only 4 studies with key limitations reported on developmental or functional outcomes (4 pre/post studies, SOE: Insufficient).

Summary of Findings: Surgery

Below we provide a summary of evidence in three categories of surgical intervention: hemispherectomy/hemispherotomy, other resections (intralobar, lobar, multilobar, focal cortical resection, posterior disconnection), and brain tumor resection. Appendix C provides detailed information regarding gender, race, seizure etiology, concomitant treatments (i.e., other ASM) and outcomes.

Hemispherectomy/Hemispherotomy

Twelve studies (reported in 13 articles) described children 1 to 36 months old undergoing hemispherectomy/hemispherotomy. Several studies described a single center's experience with performing different surgical procedures of which a subgroup of infants met our inclusion criteria. For instance, one pre/post study by Cook et al.[58] described surgical outcomes for 55 infants with cortical dysplasia undergoing hemispherectomy/hemispherotomy over a 16 year period. Sixteen of these 55 infants had hemimegalencephaly (HME) and outcomes for this subgroup are reported in Jonas et al.[59] (Authors also reported children undergoing surgery for infarction/ischemia, or Rasmussen Encephalitis; however, these groups did not meet inclusion criteria due to age). Infants underwent slightly different procedures based on year of operation: from 1986-1997 (14 anatomical hemispherectomies), from 1990-1997 (15 functional hemispherectomies), and from 1997-2002, 26 hemispherotomies).

Seizure Freedom

Eight retrospective pre/post studies[50-52,56-59,61] (reported in 9 articles[50,51,56-62]) reported on seizure freedom over a follow up period of 6 months to mean 4.3 years after surgery. Rates are presented in Figure 6. Studies included a combined 188 infants. One study (Otsuki et al.)[50] did not report follow up interval for subgroup of included patients. Three studies[58,60,61] reported seizure freedom at 6 months. Cook et al. reported a subgroup of 55 infants with cortical dysplasia undergoing anatomical hemispherectomy or functional hemispherectomy/hemispherotomy depending on the year the surgery was performed. At 6 months, 80% were seizure free. (Jonas et al. described a subset of 16 infants with HME; at 6 months 15 of 16 (93%) of these infants were seizure free). Two additional studies reported 9 of 14 (64%) [61] and 7 of 10 (70%) [60] of infants were seizure free at 6 months.

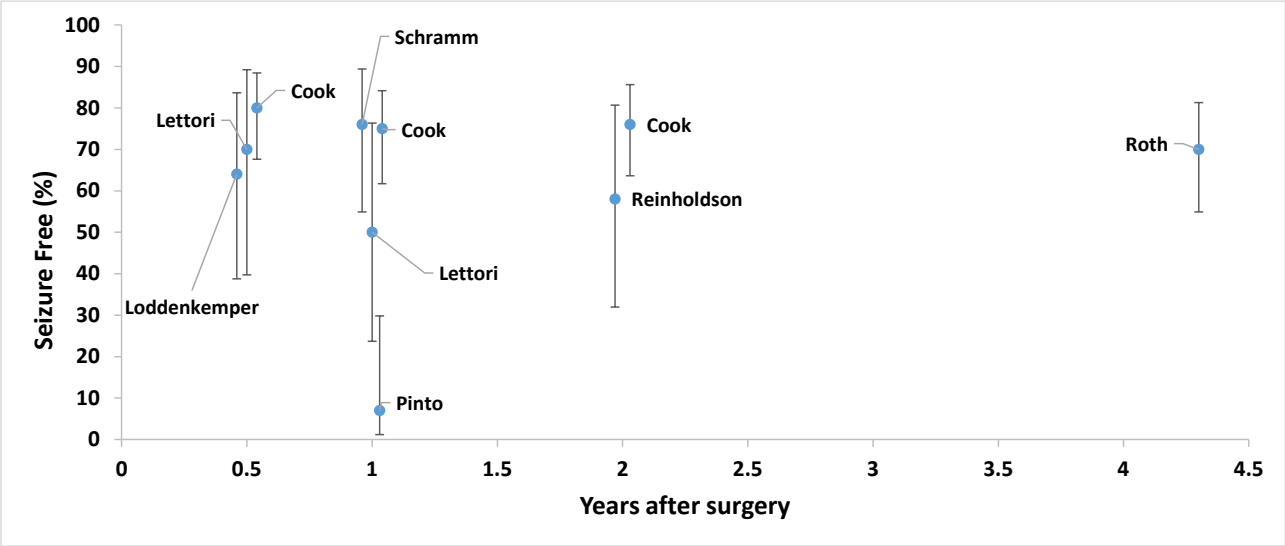
Overall, seizure free rates at 1 year or longer ranged from 7% to 76%. Six studies [51,56-58,60,62] described outcomes at 1 year or longer: Cook et al. reported 75% of infants were seizure free; other small studies reported seizure free rates of 50% (n=10) [60] and 76%[56] (n=21)[56] at one year and 58% (n=12)[51] at two years. A larger study, Roth et al.[52,62] reported at follow up median 4.3 years, 70% of patients (30 of 43) were seizure free. In contrast to these higher proportions, Pinto et al.[57] reported only 7% (1 of 15) infants were seizure free at follow up of at least 1 year after surgery.

We used stringent definition of seizure freedom which required studies using the Engel classification to report Engel Ia. However, if we had considered Engel I as seizure freedom, we note that seizure freedom from the Pinto et al. study would increase to 66% (10 of 15); also, 4

other studies[52-55] reporting rates of 55% to 81% (consistent with the range of seizure freedom rates we already identified) would have been included.

Although pre/post studies have significant limitations due to lack of control group, in these studies most infants underwent surgery for medically refractory epilepsy. Their pre-surgical status, therefore, suggests strongly that none of them would have experienced seizure freedom if they had not undergone surgery. Also, while accurately capturing seizure counts using retrospective data from charts (i.e., not captured in the context of the trial) was felt to be a key study limitation, we felt seizure freedom would be much less subject to recall bias or other types of bias. The precise rates of seizure freedom varied greatly among studies. Thus, we conclude that some infants with medically refractory epilepsy achieve seizure freedom after hemispherectomy, and we rated the strength of the evidence as Low.

Figure 6. Seizure freedom rates after hemispherectomy or hemispherotomy



The vertical bars display 95% confidence intervals. When multiple studies reported the same followup times, we used horizontal offsets to improve visibility. For studies only reporting a minimum follow up interval (e.g., follow up >1 year after surgery) data were plotted at that minimum timepoint. Of note, Otsuki et al. was not included as the study did not report the follow-up duration for this subgroup. 95% confidence intervals are shown for each data point. All studies were pre/post studies, so the precise cause of seizure freedom cannot be easily determined

Seizure Frequency

Nine retrospective pre/post studies including a combined 186 infants reported on seizure frequency. Study follow up times were variably reported with some studies including a minimum follow up time (e.g., <1 year) while for other studies, follow up was determined using individual patient data often with wide ranges. All studies reported that over half of infants achieved a favorable outcome, defined as Engel I or II, ILAE I to IV, or >50% seizure reduction. Overall, the proportion of infants achieving favorable outcome ranged from 67% to 100%, with most studies reporting follow up of at least 1 year. Specifically, studies reported the following proportion of infants had favorable outcomes at follow up: 67% (10/15),[57] 72% (13/18),[50] 73% (35/48),[53] 72% (31/43),[62] 80% (8/10),[55] 88% (14/16),[54] 92% (11/12),[51] 93% (13/14)[61] and 100% (10/10).[60] However, given the retrospective study design the outcome of seizure frequency was assessed as high risk of bias, and thus, evidence was insufficient to draw a conclusion.

Eight studies[54,55,60,61,63-65] reported individual patient data for pathology or etiology, surgical intervention, and outcomes. Surgeries reported in these studies were performed over nearly four decades (from 1979 to 2017). Unfortunately, many factors precluded formal meta-analysis, including heterogeneity across patients and interventions, and inconsistent data reporting. However, as favorable outcome after epilepsy surgery could depend on a number of factors, including underlying seizure etiology, we summarize data from 65 infants undergoing hemispherectomy or hemispherotomy. Seizure etiology or pathology was reported as HME (58%), focal cortical dysplasia (FCD) or malformation of cortical development (MCD) without HME (20%) or other (22%) (pathology or etiologies in the "other" category include stroke, subpial gliosis, Sturge Weber syndrome, and polymicrogyria). Our analysis found the proportion of infants achieving favorable outcomes was similar across these three groups: specifically, favorable outcomes were 89% (34/38) for HME, 92% (12/13) for FCD/MCD without HME, and 93% (13/14) for other pathology.

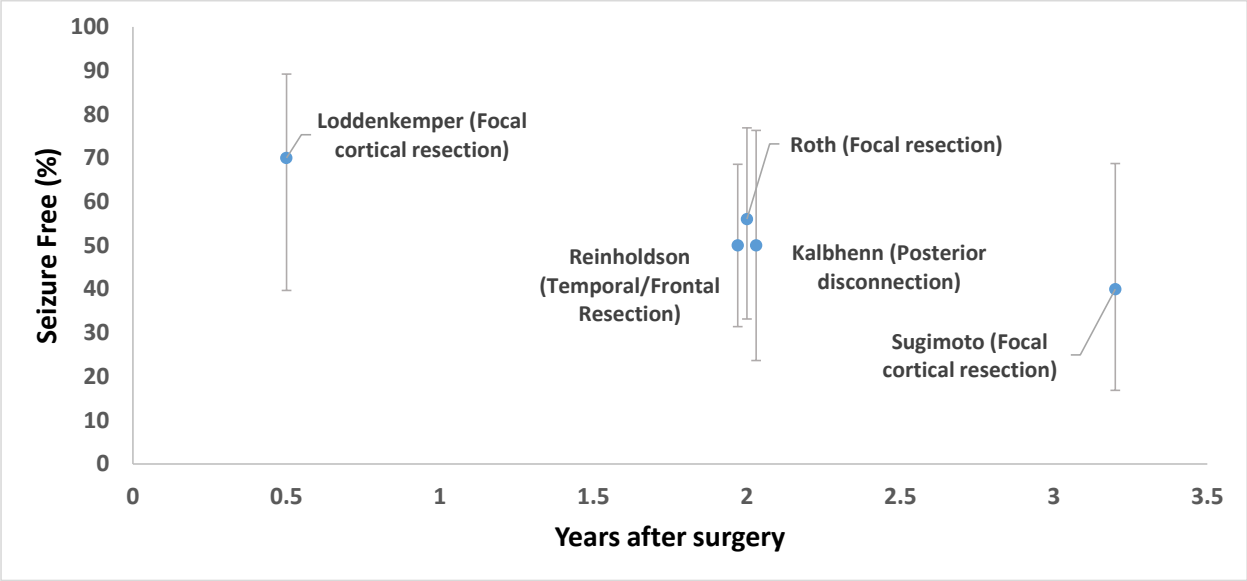
Other Resective Surgical Procedures

Eight retrospective pre/post studies reported outcomes for infants undergoing non-hemispheric procedures. Five studies reported on seizure freedom, and 7 studies on seizure frequency.

Seizure Freedom

Five pre/post studies including a combined 70 infants reported on seizure freedom. Specifically, infants underwent focal cortical resections[61-63] (n=3), frontal or temporal lobe resection[51] (n=1), [52] and posterior disconnection[64] (n=1). Rates of seizure freedom ranged from 40% (Sugimoto et al.) to 70% (Loddenkemper et al.). Figure 7 presents seizure freedom rates and follow up durations. Specifically, after focal resection studies reported seizure freedom of 70% (7/10)[61], 56% (9/16)[62], and 40% (4/10)[63], at median 6 months, 24 months, and mean 3.2 years, respectively. Kalbhenn et al.[64] reported 50% (5/10) of patients were seizure free after posterior disconnection surgery at 2 years after surgery. Reinholdson et al. reported 50% (12/24)[51] seizure freedom for infants undergoing [52] frontal or temporal lobe resection [515251] at 2 years after surgery.

Figure 7. Seizure freedom rates after other resection



The vertical bars display 95% confidence intervals. When multiple studies reported the same followup times, we used horizontal offsets to improve visibility. For studies that only reported a minimum follow up interval (e.g., follow up >1 year after surgery) data were plotted at that minimum timepoint. 95% confidence intervals are shown for each data point. Procedures represented are Loddenkemper (focal cortical resection), Reinholdson (temporal/frontal resection), Kalbhenn (posterior disconnection), Sugimoto (focal cortical resection), Roth (focal resection). All studies were pre/post studies, so the precise cause of seizure freedom cannot be easily determined

Seizure Frequency

Seven retrospective pre/post studies including a combined 148 infants reported on seizure frequency. Six of seven studies (combined n=131) reported seizure frequency data that allowed for determination of favorable outcome.[51,53,61-63,65] All studies found that ≥ 50% of infants achieved a favorable outcome, defined as Engel I or II, ILAE I to IV, or >50% seizure reduction. Specifically, the proportion of infants achieving favorable outcomes was 50% (5/10),[63] [62] 83% (20/24),[51] 85% (11/13),[65] and 90% (52/58),[53] 94% (15/16)[62], 100% (10/10)[61]. Mean follow up was at least 1 year after surgery for all studies.

A seventh study (Kadish et al.)[52] reported that of 17 infants for whom the extent of final resection was intralobar, 76% (13/17) were Engel I, while 24% (4/17) were Engel II to IV.

As previously noted, 8 studies included individual patient information regarding seizure etiology/pathology, surgical procedure, and outcomes; these studies included 43 infants undergoing multilobar, lobar, or focal resection. Seizure etiology or pathology was FCD/MCD without HME (56%) or other (44%), which included encephalitis, ganglioma, astrocytoma, tuberous sclerosis, and white matter gliosis. Our analysis found the proportion of infants with favorable outcome rates was 67% (16/24) for FCD / MCD without HME and 74% (14/19) for other pathologies.

Tumor Resection

We identified 1 study Gaggero et al. 2009[66] focused exclusively on infants with epilepsy due to brain tumors. Authors performed a retrospective chart review of infants < 3 years referred to a single center (G. Gaslini Children's hospital, Genoa Italy) for primary supratentorial brain

tumors. Tumor location was cortical in 16, non-cortical in 4. Histologic tumor types included WHO Grade I (n=5) Grade II (n=4), Grade III (n=7), and Grade IV (n=5). Twenty children had epilepsy as a clinical manifestation with focal (n=12), generalized (n=8) and history of convulsive status epilepticus (n=5). Pre-surgery, ASM use was as follows: 1 ASM (n=9), 2 ASM (n=7), and 3 ASM (n=4). Eight had received chemotherapy, and 3 had received radiotherapy. Mean time from tumor diagnosis to surgery was 0.86 (standard deviation [SD] 0.63) months.

Post-surgical follow-up ranged from 4 to 10 years (mean 7.6, SD (3.74). We report seizure freedom rates described in the study here; however, because study authors did not appear to define seizure freedom as Engel IA, data from this study were not included in analysis of seizure freedom rates).

At 1 year after surgery, 9 of 20 patients (45%) were seizure free (of which 5 were off ASM). Seven had >90% improvement in seizure frequency (Engel II), two had >50% but <90% improvement (Engel III), and 2 had no change (Engel IV). At 4 years after surgery, 11 patients were seizure free (7 off ASM), 5 had only rare seizures (Engel II), 2 had worthwhile improvement (Engel III), and 2 had no change (Engel IV). Malignancy grade (but not histological diagnosis) was associated with seizure outcomes: specifically, children with low grade tumors were more likely to have a good outcome (Engel I or Engel II), p<.001, t=2.84). Three patients died from tumor recurrence within 4 to 4.5 years (2 choroid plexus carcinomas, 1 glioblastoma multiforme). Of 17 patients with follow-up at 8 years post-operative, 9 were seizure free (Engel I), 4 (Engel II), 2 (Engel III), and 2 (Engel IV).

Other Outcomes (All Procedures)

Only 4 pre/post studies reported on developmental outcomes (developmental quotient [DQ], language or functional status). Two studies reported DQ after hemispherectomy. Loddenkemper et al.[61] included 24 infants undergoing hemispherectomy or focal resection (median age at surgery was 14 months [3 to 34]). Infants were evaluated at median 12 months (3 to 34) preoperatively, and median 24 months (10 to 53) after surgery using the Bayley scale. Although the proportion of infants with developmental delay (defined as DQ <70) decreased after surgery, this change was not statistically significant (p=0.125). However, of note, authors excluded 26 of 50 consecutive infants (due to incomplete data or use of other neuropsychological tests), limiting the generalizability of these findings. Another study (Jonas et al.)[59] found that in 16 infants undergoing hemispherectomy for HME, the Vineland DQ increased by 9.1 (SD 16) at 24 months (compared to 6 months). The spoken language rank also increased from 0.33 (SD 0.5) to 1.4 (SD 1.8) after surgery.

One study (Lettori[60]) included 10 infants meeting inclusion criteria and undergoing hemispherectomy. Before surgery functional status of 2/10 infants was dependent (and status could not be assessed for 8/10). However, after surgery, functional status improved (6 dependent, 3 semi-independent, 1 independent). Finally, 1 study (Sugimoto et al.[63]) reported some infants had improvement in developmental delay after undergoing focal cortical resection (8/10 with delay pre-operatively, 6 infants with improved or good status after surgery). However, the study did not report how delay was assessed.

Strength of Evidence: Surgery

SOE ratings for surgery appear in Table 8.

Table 8. Strength of evidence for Key Question 2: Surgical interventions

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Hemispherectomy/Hemispherotomy	Seizure Freedom	8 retrospective pre/post studies[50-52,56-59,61] reported in 9 articles[50,51,56-62] (combined n=188) At 6 months to mean 4.3 years after surgery; NR for 1 study (Otsuki) Cook: 55 infants with cortical dysplasia: 80% seizure freedom at 6 months; 75% at 1 year; subset of 16 patients reported by Jonas (at 6 months: 15 of 16 (93%) seizure free; at 1 year 14 of 16) Loddenkemper: (9 of 14 (64%) seizure free at median 6 months after surgery) Otsuki: ILAE 1: 12 of 18 66% cortical dysplasia, timepoint NR Schramm: 16 of 21 (76%) seizure free, f/u at least 1 year	High	Direct	Consistent	Precise	None	None	Low	Some infants with medically refractory epilepsy achieve seizure freedom.

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
		Reinholdson: 7 of 12 (58%) seizure free 2 years after surgery Lettori: 5 of 10 (50%) seizure free at 1 year Roth: 30 of 43 (70%) at median 4.3 years Pinto: 1 of 15 (7%) seizure free, f/u at least 1 year								
Hemispherectomy/Hemispherotomy	Seizure Frequency (Favorable Outcome defined as Engel I/II, ILAE I to IV, or >50% reduction in seizures)	9 pre/post studies[50,51,53-55,57,60-62] reported on this outcome (combined n=186)[a] Iwasaki: 80% (8/10), mean 4.2 years Kumar: 88% (14/16), mean 4.6 years Lettori: 100% (10/10), 1 year Loddenkemper: 93% (13/14), median 6 months Otsuki: 72% (13/18), f/u NR Pinto: 67% (10/15), ≥ 1 year Reinholdson: 92% (11/12), 2 years	High	Direct	Consistent	Precise	No	No	Insufficient	N/A

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
		Roth: 72% (31/43), median 51 months Steinbok: 73% (35/48), ≥ 1 year								
Other Resections (intralobar, multilobar, posterior disconnections	Seizure Freedom	5 pre/post studies [51,61-64] combined (n=70) Loddenkemper (focal cortical resection) 70% (7/10), median 6 months (4 to 42) Reinholdson (Frontal/temporal lobe resection, 50% (12/24), 2 y Sugitomo (focal cortical resection, 40% (4/10), mean 3.2 years, range (0.25 to 6.7 y) Kalbhenn (posterior disconnection, 50% (5/10), 2 y Roth (focal resection), 56% (9/16), median 24 months	High	Direct	Consistent	Precise	None	None	Low	Some infants with medically refractory epilepsy achieve seizure freedom.
Other Resections (intralobar, multilobar, posterior disconnections	Seizure Frequency (Favorable outcome, defined as Engel I/II, ILAE I to IV,	6 pre/post studies[51,53,61-63,65](n=131) Proportion of infants achieving favorable outcome ranged	High	Direct	Consistent	Precise	None	None	Insufficient	NA

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
	or >50% reduction in seizures)	from 50% to 100%. Loddenkemper (focal resection), 100% (10/10), median 6 months after surgery Maton (temporal lobe resection, 85% (11/ 13), mean 6.3 y after surgery Reinholdson (temporal/frontal resection, 83% (20/24), 2 y after surgery Roth (focal resection/lobectomy, 94% (15/16), median 24 months after surgery) Steinbok (lesionectomy/cortical resection), 90% (52//58), 1 y or more after surgery) Sugimoto (focal cortical resection, 50% (5/10), 3.2 y, range 0.25 to 6.7 after surgery)								
Resection of Supratentorial Brain tumor causing epilepsy	Seizure Frequency	One pre/post study[66] (n=20) At 1 and 4 years after surgery 80%	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
		(16 of 20) children were Engel I or II. 8 years after surgery, 13 of 17 children that remained alive were Engel I or II.								

NA = Not applicable; NR = Not reported; f/u = followup

[a] Some included in Roth et al.[62] may have been previously reported in Loddenkemper et al.[61] Thus, the total number of unique patients may be lower for outcomes drawing data from both of these studies.

Key Question 3. What are the harms or comparative harms of treatments for infantile epilepsies?

Description of Included Evidence

Table 9 lists the studies included for this Key Question.

Table 9. Overview of included studies for Key Question 3

Treatment	Treatment Comparison	Study	Design
Levetiracetam	None	Arzimanoglou et al. (2016)[32]	Pre/Post
Levetiracetam	None	Arican et al. (2018)[34]	Pre/Post
Levetiracetam	Valproate vs Valproate + Levetiracetam	Liu et al. (2020)[33]	RCT
Topiramate	Topiramate vs Carbamazepine	Kim et al. (2009)[36]	Non-randomized comparative study
Topiramate	None	Kim et al. (2010)[67]	Pre/Post
Topiramate	3 vs 5 vs 15 vs 25 mg/kg/day	Manitpisitkul et al. (2013)[68]	RCT
Topiramate	Placebo vs 5 vs 15 vs 25 mg/kg/day	Novotny et al. (2010)[69,70]	RCT
Lamotrigine	Continued lamotrigine vs substituted placebo	Piña-Garza et al. (2008)[30,38]	Withdrawal RCT
Phenytoin	None	Sicca et al. (2000)[39]	Pre/Post
Vigabatrin	None	Jackson et al. (2017)[31]	Pre/Post
Rufinamide	None	Tanritanir et al. (2021)[40]	Pre/Post
Stiripentol	None	Yamada et al. (2021)[41]	Pre/Post
Ketogenic diet	None	Kim et al. 2019[46]	Pre/Post
Ketogenic diet	None	Dressler et al. (2015)[47]	Pre/Post
Ketogenic diet	None	Liu et al. 2021[49]	Pre/Post
Ketogenic diet	Ketogenic diet vs Modified Atkins Diet vs Normal diet	El-Rashidy et al. 2013[42]	RCT
Hemispherectomy/ hemispherotomy	None	Otsuki et al. 2013[50]	Pre/Post
Hemispherectomy/ Hemispherotomy	None	Reinholdson et al. 2015[51]	Pre/Post
Hemispherectomy/ Hemispherotomy	None	Kadish et al. 2019[52]	Pre/Post
Hemispherectomy/ Hemispherotomy	None	Steinbok et al. 2009[53]	Pre/Post
Hemispherectomy/ Hemispherotomy	None	Dunkley et al. 2010[71]	Pre/Post
Hemispherectomy/ Hemispherotomy	None	Kumar et al. 2015[54]	Pre/Post
Hemispherectomy/ Hemispherotomy	None	Iwasaki et al. 2015[55]	Pre/Post
Hemispherectomy/ Hemispherotomy	None	Pinto et al. 2014[57]	Pre/Post

Treatment	Treatment Comparison	Study	Design
Hemispherectomy/ Hemispherotomy	None	Cook et al. 2004[58]	Pre/Post
Hemispherectomy/ Hemispherotomy	None	Lettori et al. 2007[60]	Pre/Post
Hemispherectomy/ Hemispherotomy	None	Roth et al. 2021[62]	Pre/Post
Hemispherectomy/ Hemispherotomy	None	Iwasaki et al. 2021[72]	Pre/Post
Other resective surgery	None	Dunkley et al. 2010[71]	Pre/Post
Other resective surgery	None	Kalbhenn et al. 2019[64]	Pre/Post
Other resective surgery	None	Roth et al. 2021[62]	Pre/Post
Other resective surgery	None	Iwasaki et al. 2021[72]	Pre/Post
Combined data on multiple surgical procedures	None	Steinbok et al. 2009[53]	Pre/Post

RCT = Randomized controlled trial

Key Points

- Levetiracetam is rarely discontinued due to adverse effects (SOE: Low)
- Topiramate is rarely discontinued due to adverse effects, and severe events are rare (SOE: Low). However, loss of appetite and upper respiratory tract infection are risks (SOE: Moderate)
- Lamotrigine is rarely discontinued due to adverse effects, and severe events are rare (SOE: Low)
- Only four of the eight studies of dietary interventions reported whether there were harms for those age 1-36 months, and the data were too sparse to permit conclusions (SOE: Insufficient)
- Surgical mortality for functional hemispherectomy/hemispherotomy is rare (SOE: Low)
- Evidence is insufficient to draw a conclusion regarding mortality after anatomical hemispherectomy (SOE: Insufficient)
- Surgical mortality for multilobar, unilobar, or focal resection is rare (SOE: Low)
- Hydrocephalus requiring shunt placement after multilobar, unilobar, or focal resection is rare (SOE: Low)

Summary of Findings

Harms of Levetiracetam

One nonrandomized comparison study[36] and two pre/post/studies[32,34] reported adverse event data for levetiracetam. Please see Key Question 1 for summaries of their enrolled patients and treatment details.

We first discuss the reported data on levetiracetam discontinuation due to adverse events including “serious” events, “severe” events, or events requiring dose modification. We then

summarize any adverse events that occurred in 10% or more of patients who received levetiracetam. Appendix C provides all adverse event data (including those with rates <10%).

Arzimanoglou et al. (2016)[32] administered levetiracetam at a mean daily dose of 46 mg/kg/day. At least one treatment-emergent adverse event led to study discontinuation in 7% of patients (7/101). The specific events were respiratory disorder (2 patients), respiratory distress and infantile spasms (two patients), irritability (one patient), lower respiratory tract infection, psychomotor retardation (one patient), and respiratory failure (one patient). Also, 12% of patients (12/101) had a "severe" treatment-related adverse event, but authors stated that none were considered related to levetiracetam by the clinician. "Serious" events occurred in 32% (32/101), but only two of them (both convulsions) were considered levetiracetam-related (authors did not define the difference between "severe" and "serious"). Furthermore, 10% (10/101) had an adverse event that required dose modification.

Arican et al. (2018)[34] reported that among 92 patients taking levetiracetam 10-60 mg/kg/day (52% on 30-40 mg/kg/day), no patients discontinued due to adverse events. The study made no statements about serious or severe events or any events requiring dose modification.

Liu et al. (2020)[33] reported an RCT comparing valproate alone (40-50 mg/kg/day) to valproate + levetiracetam (20-30 mg/kg/day). The study did not explicitly report whether any infants discontinued levetiracetam due to adverse events, whether any events were severe/serious, or whether any dose modifications were necessary. Effectiveness data were reported for all enrolled patients at 12 weeks, so likely there were no <12-week discontinuations due to adverse events.

Regarding non-severe events experienced by at least 10% of patients, the only pertinent events were bronchitis (10% as reported by Arzimanoglou et al. (2016)[32]) and convulsion (10% as reported by Arzimanoglou et al. (2016)[32]).

Overall, the only small signal from these data involve possible respiratory harms of levetiracetam (as per the study discontinuations in Arzimanoglou et al. (2016)[32]). However, neither of the other two studies reported any respiratory events.

Harms of Topiramate

Four studies of topiramate reported data on harms: two RCTs,[68,70] one nonrandomized comparative study,[36] and one pre/post study.[67] Both RCTs compared different doses of topiramate: Novotny et al. (2010)[69,70] compared placebo to three different doses (5 or 15 or 25 mg/kg/day; 37-38 infants per group), while Manitpisitkul et al. (2013)[68] compared four different doses (3 or 5 or 15 or 25 mg/kg/day; 13-15 infants per group). Dose comparisons are particularly informative, because the medication-harm causal connection is stronger if there is a clear dose-response association. Conversely, the absence of a no dose-response association reduces the likelihood that the medication causes the harm. We first discuss events causing medication discontinuation, then severe/serious events and dose modifications, and finally, events experienced by 10% or more of infants.

Reported harms in three of the four studies are summarized in Table 10 (the fourth study only reported hypohydrosis, so we discuss its results separately). For discontinuation due to adverse events as well as serious/severe events, rates were low in all three studies, with no dose-response association. For less severe events (occurring in at least 10% of patients) the two RCTs found dose-response associations for loss of appetite and upper respiratory tract infection. For three other less severe events, one RCT found a dose-response association, but the other RCT did not. For seven other less severe events, neither RCT showed a dose-response association (coughing,

diarrhea, fever, viral infection, somnolence, otitis media, and rhinitis). Kim et al. (2009)[36] also reported a rate of 17% (7/41) for psychomotor retardation

The pre/post study by Kim et al. (2010)[67] focused only on the risk of hypohydrosis with topiramate, and authors had performed a subgroup analysis of 81 infants age 1 year or less. The rate of hypohydrosis in these infants was 48% (39/81). The only other study to mention this type of event was Kim et al. (2009),[36] which reported a rate of "anhidrosis" of 2% (1/41) (far lower than the 48% reported by Kim et al. 2010).[67]

Overall, these adverse event data suggest topiramate is not difficult to tolerate. We did find consistent evidence for two non-severe adverse events with topiramate: loss of appetite (7%-20% with risk increasing with dose) and upper respiratory tract infection (8%-38% with risk increasing with dose).

Table 10. Summary of harms of topiramate

Type of Harm	RCT, Novotny et al. (2010)[69,70]	RCT, Manitpisitkul et al. (2013)[68]	CT, Kim et al. (2009)[36]
Discontinuation due to adverse events	3-5% in all four groups	1/x in the 5 mg/kg/day group and 2 in the 15 mg/kg/day group	12% (5/41)
Serious/severe events	3 infants in each of the 4 groups	2 infants in each of 3 dose groups (3, 5 and 25 mg/kg/day)	No events occurred
Consistent dose-response association: Loss of appetite	5% rate with placebo 11% rate with 5-15 mg/kg/day 16% rate with 25 mg/kg/day	7% rate with 3 mg/kg/day 8% rate with 5-15 mg/kg/day 20% rate with 25 mg/kg/day	2% rate
Consistent dose-response association: Upper respiratory tract infection	14% rate with placebo 21% rate with 5 mg/kg/day 22% rate with 15-25 mg/kg/day	0% rate with 3 mg/kg/day 8% rate with 5 mg/kg/day 15% rate with 15 mg/kg/day 38% rate with 25 mg/kg/day	NR
Inconsistent dose-response association: Bronchitis	0% rate with placebo 8% rate with 5 mg/kg/day 3% rate with 15 mg/kg/day 8% rate with 25 mg/kg/day	0% rate with 3-5 mg/kg/day 8% rate with 15 mg/kg/day 13% rate with 25 mg/kg/day	NR
Inconsistent dose-response association: Vomiting	5% rate with placebo 18% rate with 5 mg/kg/day 8% rate with 15 mg/kg/day 16% rate with 25 mg/kg/day	7% with 3 mg/kg/day 8% with 5 mg/kg/day 15% with 15 mg/kg/day 20% with 25 mg/kg/day	2% rate
Inconsistent dose-response association: Weight decrease	3% rate with placebo 0% rate with 5 mg/kg/day 5% rate with 15 mg/kg/day 14% rate with 25 mg/kg/day	0% with 3/5/15 mg/kg/day 13% with 25 mg/kg/day	NR

CT- Controlled trial
NR – Not reported
RCT- Randomized controlled trial

Harms of Lamotrigine

Piña-Garza et al. (2008)[30,38] studied lamotrigine and reported three sets of data: the initial open label phase (N=177) for at least five 5 weeks, the RCT phase comparing continued lamotrigine to replacement of lamotrigine with placebo for eight weeks (N=19 per group), and the long-term open label phase (at least 24 weeks in 92% of infants; N=204). All harms data from these sets appear in Appendix C. In this section, we discuss only the RCT phase and the long-term open label phase (due to its larger N than the initial open label phase).

During the eight-week randomized phase, none of the 38 patients had lamotrigine discontinued due to adverse events; this may be because the only infants who entered this phase had demonstrated tolerance during the initial five-week open label phase. In the long-term open label phase, 9% of patients (18/204) had lamotrigine discontinued due to adverse events. The authors reported specifics for 15 of 18 discontinuations: pneumonia (n = 4), complex partial seizures (n = 3), status epilepticus (n = 3), rash (n = 3), and fever (n = 2).

Regarding serious events, two events occurred in the randomized phase: one lamotrigine patient (5%, 1/19) had serious bronchitis, and one placebo patient (5%, 1/19) had status epilepticus. During the long-term open label phase with lamotrigine, 8% had pneumonia (16/204), 6% (12/204) had status epilepticus, 6% (12/204) had complex partial seizures, 4% (12/204) had fever, 3% (6/204) had convulsion, 3% (6/204) had dehydration, and 3% (12/204) had gastroenteritis.

For non-serious events, the RCT phase had five events in which one of the two groups had rates of 10% of more (cough, nasal congestion, upper respiratory tract infection, fever, and teething). The long-term open label phase had 15 events with rates of 10% of more: fever, upper respiratory tract infection, ear infection, cough, vomiting, otitis media, irritability, constipation, nasopharyngitis, teething, rash, bronchitis, pneumonia, status epilepticus, upper respiratory tract congestion. See Appendix C for the rates of these events.

Overall, the most common adverse events reported with lamotrigine are fever (45%), upper respiratory tract infection (28%), and ear infection (22%). Left untreated, some of these events may later be associated with pneumonia, as 8% had lamotrigine discontinued for that reason.

Harms of Phenytoin

The pre/post study by Sicca et al. (2000)[39] enrolled 55 infants who had received oral phenytoin for seizure prophylaxis. The study reported neither phenytoin discontinuation due to adverse events nor any "serious" or "severe" harms of phenytoin. Of less severe events, only four had rates of 10% or more:

- Drowsiness: 22% (12/55)
- Gingival hyperplasia: 15% (8/55)
- Sleep troubles: 15% (8/55)
- Hyperactivity: 11% (6/55)

Although drowsiness is fairly common (22%), in general, these data are too sparse to draw clear conclusions regarding the adverse effects of oral phenytoin when administered to infants.

Harms of Vigabatrin

Jackson et al. (2017)[31] was a pre/post study that administered vigabatrin to 103 infants. The authors reported a rate of vigabatrin discontinuation-due-to-adverse effects of 9% (9/103), with specific reasons being vision abnormality (n=5), fatigue (n=1), fatigue and anorexia (n=1), "possible vigabatrin toxicity" (n=1), and anemia (n=1). The study did not report rates of "severe" or "serious" adverse events.

Authors reported rates of adverse events specifically for the 71 infants who discontinued vigabatrin for any reason (e.g., the reason was successful control of seizures in 31 infants, and unsatisfactory therapeutic effect in 23 infants). None of the reported events reached 10% or more (see all data in Appendix C). Authors also specifically conducted eye exams before vigabatrin (N=49), during vigabatrin (n=62), and after vigabatrin (n=49) to evaluate for vision abnormalities possibly caused by vigabatrin. The authors reported these three time periods

separately, but unfortunately did not report the number of infants whose vision status had changed between measurements (which would have more directly addressed the influence of vigabatrin).

Prior to vigabatrin administration, 69% (34/49) had vision abnormalities, which authors attributed to tuberous sclerosis complex, refractive errors, and prior medication. The study did not report which baseline medications were likely responsible for the pre-vigabatrin abnormal eye exam results. During vigabatrin, 81% (50/62) had at least one abnormal exam. After vigabatrin, 63% (31/49) had vision abnormalities.

Overall, some evidence suggests that vigabatrin may cause temporary vision abnormalities, but only a single pre/post study has addressed the issue.

Harms of Rufinamide

Tanritanir et al. (2021)[40] was a pre/post study that administered rufinamide to 103 infants. Fifteen (15%) discontinued rufinamide due to adverse effects (three of these were solely due to adverse effects, and the other 12 were due to both adverse effects and lack of efficacy). Authors did not mention whether any events were serious or severe. Rates of 10% or higher were observed for somnolence (12% or 12/103) and irritability (10% or 10/103).

Harms of Stiripentol

Yamada et al. (2021)[41] was a pre/post study that administered stiripentol to 95 infants age 0-2 years. Authors did not report the specific types of adverse reactions in these patients, but did report that 61% (58/95) had at least one adverse drug reaction. Physicians in charge determined that all 58 had a causal relationship to stiripentol (either "clearly" or "probably" or possibly"). One patient died due to liver damage, which physicians deemed a "possible" relationship to stiripentol, but the patient was also taking both valproate and clobazam.

Harms of Ketogenic Diet

Of 8 included studies of ketogenic diet, 4 reported data pertaining to harms for infants age 1-36 months.[42,46,47,49] Three[43,44,48] of the other four reported data on adverse events, but data were not specific to age 1-36 months, and the fourth study[45] did not investigate whether adverse events occurred.

Two of four studies reported the rate of withdrawal due to side effects or diet intolerance. Kim et al. 2019[46] found a rate of 2% (2/109; one behavioral food refusal and one persistent acidosis), and El-Rashidy et al. (2013)[42] found a rate of 20% (2/10; both diet intolerance).

For other reported adverse effects:

- Kim et al. (2019)[46] reported 33% of patients had decreased $HC0_3$ level (36/109), 32% constipation (35/109), , and 20% vomiting/reflux (22/109); three other events were experienced by <10% of patients.
- Dressler et al. (2015)[47] reported that 50% (29/58) of patients experienced "side effects", but authors did not report specifics. Also, for 28% (16/58) there was "difficulty introducing solid foods".
- Liu et al. (2021)[49] reported z scores of body mass index (BMI)-for-age at 3-12 months after KD initiation. For the 41 patients, the baseline mean was 0.49, which changed to 0.06 at 3 months, 0.16 at 6 months, and 0.35 at 1 year; none of these changes were statistically significant. Authors also reported statistically non-significant changes over time in the percentage of patients who were underweight (defined as weight-for-age z

score <-2), stunting (defined as height-for-age z score <-2), and wasting (defined as BMI-for-age z score <-2). However, the percentage of patients who were overweight/obese decreased (statistically significantly) from 17% at baseline to 2% at one year after KD initiation.

- El-Rashidy et al. (2013)[42] reported low rates of vomiting, constipation, diarrhea, and dysphagia (0%, 20%, 10% and 10%, respectively).

Harms of Modified Atkins Diet

One study reported harms data for Modified Atkins diet. Specifically, El-Rashidy et al. (2013)[42] reported that 13% (2/15) of patients dropped out due to diet intolerance and had experienced "significant" weight loss. Also, El-Rashidy et al. (2013)[42] reported 27% vomiting (4/15), 13% constipation (2/15), 13% diarrhea (2/15), and 20% dysphagia (3/15).

Harms of Hemispherectomy/Hemispherotomy

Eleven pre/post studies[50-55,57,58,60,62,71] reported harms after hemispherectomy/hemispherotomy including mortality, hydrocephalus, infection, and other adverse events. One study (Roth et al.[62]) included data from 19 centers with surgical procedures performed from 1999 to 2020. Seven patients cared for at 3 of 19 centers (University of California at Los Angeles, Cleveland Clinic, and Great Ormond Street Hospital) may have also been previously reported in other studies included in this report.[58,61,71] (author correspondence). A second study, Iwasaki et al. (2021)[72] described harms for 75 infants, of which 9 hemispherectomy patients had previously been described in Otsuki et al. (2013)[50] (author correspondence). Further details are provided in Appendix C.

Mortality

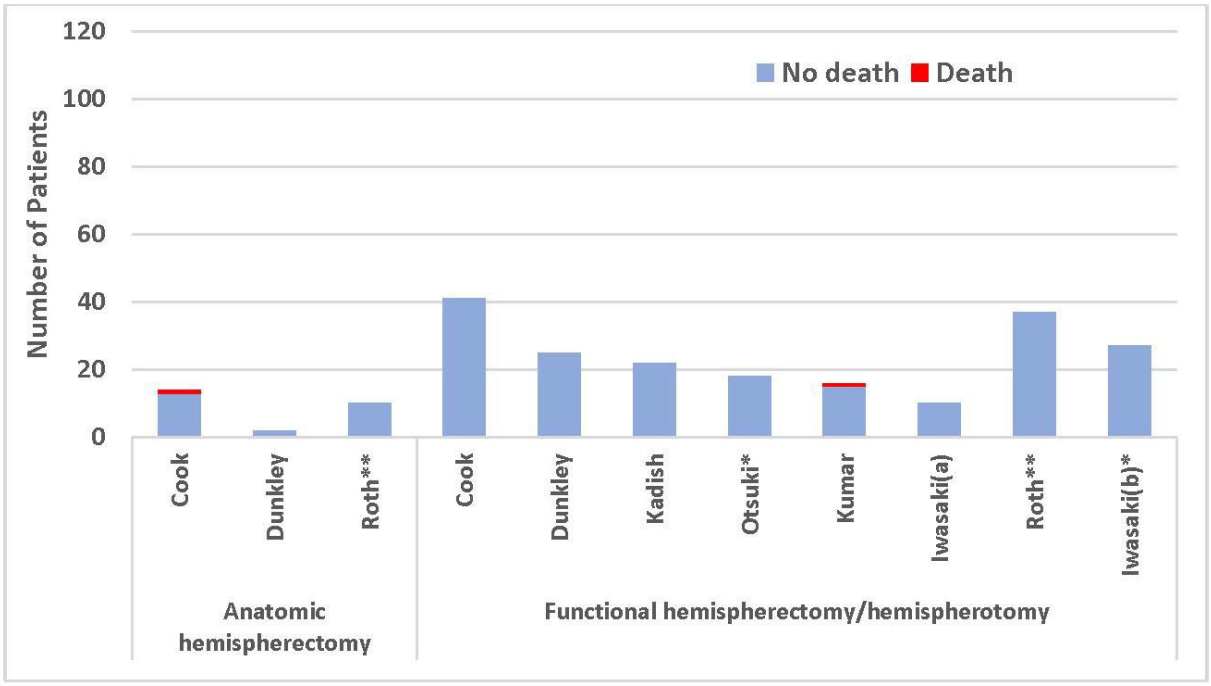
Nine pre/post studies reported on mortality after hemispherectomy/hemispherotomy (see Figure 8). Studies described mortality after anatomical hemispherectomy (n=3), functional hemispherectomy or hemispherotomy (n=8), or across multiple procedures (lesionectomy, cortical resection, and hemispherectomy/hemispherotomy, 1 study). Only 3 retrospective chart reviews reported data for infants specifically undergoing anatomical hemispherectomy: Cook et al.[58] reported that of 14 infants (operated on from 1986 to 1997 at University of California Los Angeles) there was 1 intra-operative death, an 8 month old infant with HME. Dunkley et al.[71] reported no deaths for either of the 2 infants undergoing anatomical hemispherectomy over a 10 year period (year not reported). Roth et al.[62] reported no deaths for 10 infants undergoing anatomical hemispherectomy. Given the sparse data, we deemed the evidence insufficient to permit conclusions.

Eight studies described surgical mortality for a combined 196 infants undergoing functional hemispherectomy/hemispherotomy. Seven of 8 studies (including 180 infants)[50,52,55,58,62,71,72] reported that there were no deaths; Kumar et al.[54] reported a single death of 16 hemispherotomies. The death occurred in an infant with epidermal nevus syndrome, right HME, and multiple other congenital abnormalities who developed refractory seizures after surgery and care was withdrawn.

Finally, Steinbok et al.[53] reported a single death across 116 infants undergoing 151 surgical procedures which were either a hemispherectomy/hemispherotomy, lesionectomy, or cortical resections. The intraoperative death occurred in a 3.9-month child with tuberous sclerosis undergoing attempted resection of intraventricular and extraventricular lesions.

Although limited, evidence from these studies suggests peri-operative mortality after functional hemispherectomy or hemispherotomy is uncommon. However, these studies were primarily single center retrospective chart reviews including heterogenous infants (with many different seizure etiologies), and studies often failed to specify what proportion of infants did not meet criteria for inclusion based on missing data. Furthermore, it is possible that centers with higher mortality rates might choose not to publish their data. However, despite these limitations of the evidence base, we concluded that surgical mortality after functional hemispherectomy/hemispherotomy is rare (SOE: Low).

Figure 8. Surgical mortality for hemispherectomy/hemispherotomy



*Nine infants undergoing hemispherectomy/hemispherotomy included in Iwasaki et al. 2021[72] (denoted Iwasaki[b]) were already described in Otsuki et al.[50]
**Roth et al. included data from 19 centers; 7 patients from 3 of 19 centers may also have been described in prior studies.[58,61,71]

Hydrocephalus and Other Adverse Events

Twelve studies reported other adverse events (AEs) for infants undergoing hemispherectomy/ hemispherotomy (see Table 11).

For anatomical hemispherectomy, studies reported that development of hydrocephalus/ ventriculoperitoneal shunt placement was common (see

Figure 9). Three studies (combined n=19 surgeries) reported this AE: Dunkley et al. reported that both infants (2 of 2) required a VP shunt at 12 months after surgery. Similarly, 7 of 10 infants undergoing anatomical hemispherectomy in another study (Pinto et al.[57]) required ventriculoperitoneal shunt placement. A third study (Lettori et al.[60]) reported 3 of 7 infants undergoing anatomical hemispherectomy or hemidecortication developed hydrocephalus (follow-up interval not reported).

For functional hemispherectomy or hemispherotomy, 9 studies (combined n=196, plus infants from 1 additional study only reporting a percentage[52] and 1 study with an unclear

denominator[53]) reported on this AE. Generally, studies reported lower rates of hydrocephalus/shunt placement compared to anatomical hemispherectomy. 1 of 9 studies reported no infants (0 of 10) developed hydrocephalus.[55] Another study reported 4 infants undergoing functional hemispherectomy developed hydrocephalus (at least 22 infants underwent functional hemispherotomy, but the total number of infants undergoing this procedure was unclear).[53] The remaining 7 studies reported rates of 8.3% (1 of 12),[51] 11% (3 of 27),[71] 16% (Kadish et al.[52]), 20% (1 of 5),[57] 22% (6 of 27),[72] 25% (4 of 16),[54] and 33% (1 of 3).[60]

Finally, Roth et al.[62] reported hydrocephalus in 25% (11 of 44) infants undergoing either anatomical hemispherectomy or functional hemispherectomy/hemispherotomy. Notably, only 1 study[71] reported when hydrocephalus occurred. Another study reported a time range (months).[53] Four studies[52,55,55,60] did not report when hydrocephalus occurred, and remaining studies provided a timepoint at which other outcomes were measured (eg. >1 year after surgery), but no other information regarding timing of hydrocephalus.

Other AEs reported for anatomical hemispherectomy include:

- Central nervous system (CNS) infection (2/14)[58]
- Deep infection (1/7)[60]
- Superficial infection (1/7)[60]
- Cranial nerve III palsy (1/14)[58]
- Inappropriate antidiuretic hormone (1/14)[58]
- Subdural fluid collection (1/7)[60]
- Cerebrospinal fluid leakage (1/7)[60]
- Transient fever (2/7)[60]

Other AEs reported for functional hemispherectomy/hemispherotomy include:

- CNS infection (2/41)[58]
- Superficial infection (1/3)[60]
- Dural adhesions requiring "late reoperation" (1/41)[58]
- Acute post-surgical seizures (23%)[52]
- Epidural hemorrhage requiring surgical revision (1/22)[52]
- Excessive bleeding (1/16)[54]
- Pituitary failure due to thalamic lesion(1/22)[52]
- Inadvertent extubation (1/16)[54]
- Intraoperative disseminated intravascular coagulation (1/37)[62]
- Cyst formation requiring surgical intervention (2/27)[72]
- Cerebral salt wasting syndrome (2/27)[72]
- Diabetes insipidus (3/27)[72]
- Sinus thrombosis (resulting from diabetes insipidus) (2/27)[72]
- Asymptomatic hemorrhagic infarction (1/27)[72]

Finally, two studies reported combined AEs for multiple procedure types. One study (Steinbok et al[53]) reported AEs for procedures including anatomical hemispherectomy, hemidecortication, functional hemispherectomies, and peri-insular hemispherotomies: 31 of 40 infants required blood transfusion, and 13 infants developed perioperative aseptic meningitis which was successfully managed with steroids.

A second study (Roth et al.[62]) reported AEs for a total 69 procedures which included hemispheric and non-hemispheric surgeries. However, with the exception of one AE (disseminated intravascular coagulation), remaining AEs were not reported by procedure.

Table 11. Surgical studies reporting harms

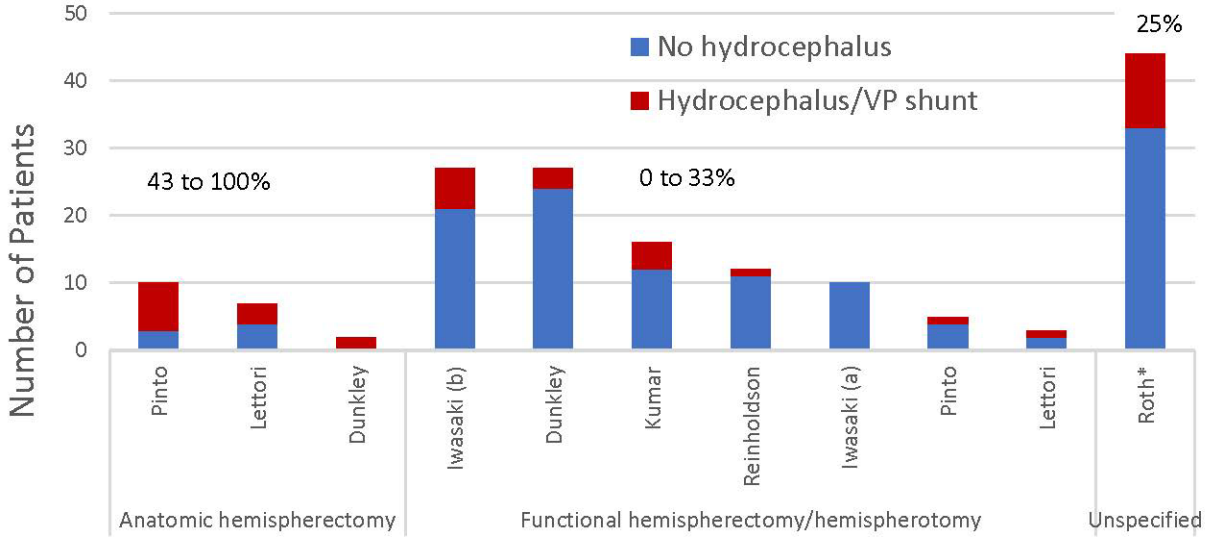
Surgery	Surgery Type	Mortality	Hydrocephalus and Other Adverse Events
Hemispherectomy/ hemispherotomy	Anatomical hemispherectomy	Cook et al.[58] Dunkley et al.[71] Roth et al.[62]	Cook et al.[58] Dunkley et al.[71] Lettori et al.[60] Pinto et al.[57]
Hemispherectomy/ hemispherotomy	Functional Hemispherectomy/Hemispherotomy	Cook et al.[58] Dunkley et al.[71] Iwasaki et al.[55] Kadish et al.[52] Kumar et al.[54] Otsuki et al.[50a] Roth et al.[62] [b] Iwasaki et al.[72] [a]	Cook et al.[58] Dunkley et al.[71] Iwasaki et al.[55] Kadish et al.[52] Kumar et al.[54] Lettori et al.[60] Pinto et al.[57] Reinholdson et al.[51] Roth et al.[62] [b] Iwasaki et al.[72] Steinbok et al.[53] [c]
Other Resections	Multilobar/lobar/focal resection or Posterior Disconnection	Dunkley et al.[71] Iwasaki et al.[72] Roth et al.[62] [b]	Dunkley et al.[71] Kadish et al.[52] Kalbhenn et al.[64] Iwasaki et al.[72] Roth et al.[62] [b] Steinbok et al.[53] [c]
Study reported combined outcome for multiple procedures	Infants undergoing lesionectomy, cortical resection, or hemispheric surgery	Steinbok et al.[53]	Steinbok et al.[53]

[a]Nine infants undergoing hemispherectomy/hemispherotomy included in Iwasaki et al. 2021[72] were already described in Otsuki et al.[50]

[b]Roth et al. included data from 19 centers; 7 patients from 3 of 19 centers may also have been described in prior studies.[58,61,71]

[c]Steinbok reported hydrocephalus for functional hemispherectomy and cortical resection, but other harms were only reported across all procedures.

Figure 9. Rates of hydrocephalus after hemispherectomy/hemispherotomy



*Roth et al. included data from 19 centers; for hydrocephalus, 1 patient may have been previously described in Dunkley et al.[71] Data from Kadish et al, is not shown here as authors only reported the rate of hydrocephalus; Data from Steinbok are not shown as authors did not report the total number of hemispherectomies/hemispherotomies for this outcome. Note: Only 1 study (Dunkley et al.) provided information regarding when hydrocephalus occurred. Five studies (Iwasaki 2015, Iwasaki 2021, Kadish et al., Lettori et al., and Pinto et al.) provided no information about timing. Remaining studies only described a timepoint at which other outcomes in the study were measured.

VP = ventriculoperitoneal

Harms of Other Resective Surgical Procedures

Mortality

Four pre/post studies described surgical mortality for infants undergoing non-hemispheric procedures. Three studies[62,71,72] described surgical mortality for a combined 82 infants undergoing multilobar, lobar, or focal resections. All 3 studies reported no deaths.

Studies described a range of procedures. Dunkley et al.[71] included 15 infants undergoing either multilobar, lobar, or focal resections. Iwasaki et al. 2021[72] included 48 infants undergoing multilobar or unilobar surgeries. Multilobar procedures included 13 posterior quadrantic disconnections, 5 multifocal cortical resections, 1 subtotal hemispherotomy; unilobar procedures included 16 focal cortical resections or lesionectomies, 8 anterior temporal lobectomies, 5 frontal lobectomies or disconnections. A third study by Roth et al.[62] included 19 infants undergoing focal resections. Finally, Steinbok et al.[53] reported a single mortality across 116 infants undergoing 151 procedures which were either a hemispherectomy/hemispherotomy, lesionectomy, or cortical resections. (As previously noted, Roth et al. included 1 patient that may have been previously reported in Dunkley et al.[71])

This evidence base is small with important limitations. For instance, all studies were retrospective pre/post studies and 2 studies reported experience drawn from only single centers. However, results from Roth et al. (which included data from 19 centers) were consistent in also reporting no deaths. Another consideration is that reported mortality rates may be artificially low if centers with higher mortality rates choose not to publish their data. Nevertheless, despite these

limitations, we concluded that surgical mortality after multilobar, lobar, or focal resection is rare (SOE: Low).

Hydrocephalus and Other Adverse Events

Five studies reported on infants undergoing focal, intralobar, or multilobar resections. Four studies (Dunkley et al.,[71] Kadish et al.,[52] Roth et al.,[62] Iwasaki et al.[72]) with a combined 108 procedures) reported that no patients developed hydrocephalus (follow up duration not reported for 3 studies,[52,71,72] and the 4th reported all study outcomes at a median 24 months.[62] A fifth study (Steinbok et al.[53]) reported 3 infants undergoing cortical resection developed hydrocephalus within a few months after surgery, but the total number of infants undergoing non-hemispheric procedures was unclear.

Two studies reported AEs other than hydrocephalus. A single German study (Kalbhenn et al. 2019)[64] included 10 infants undergoing posterior disconnection for refractory posterior quadrantic epilepsy. Authors reported a single patient developed transient hemiparesis. A second Japanese study (Iwasaki et al. 2021[72]) reported the following complications requiring surgical or medical intervention in 48 infants undergoing multilobar, unilobar, or focal resections: subdural hygroma (n=3), cyst formation (n=2), asymptomatic cerebral infarction (n=1), bacterial meningitis (n=1), and psychiatric symptoms (n=1).

Strength of Evidence

Our strength of evidence (SOE) ratings for Key Question 3 appear in Table 12. The evidence permits the following conclusions about the harms of pharmacologic treatments:

- Levetiracetam is rarely discontinued due to adverse effects (SOE: Low)
- Topiramate is rarely discontinued due to adverse effects, and severe events are rare (SOE: Low). However, loss of appetite and upper respiratory tract infection are risks (SOE: Moderate)
- Lamotrigine is rarely discontinued due to adverse effects, and severe events are rare (SOE: Low)

Other adverse effects data for pharmacologic treatments were insufficient to permit conclusions, primarily due to risk of bias in pre/post studies, inconsistency, and imprecision.

With regard to surgical interventions, we concluded the following:

- Surgical mortality is rare after functional hemispherectomy/hemispherotomy (SOE: Low)
- Surgical mortality is rare after multilobar, unilobar, or focal resections (SOE: Low).
- Evidence is insufficient to permit conclusions regarding surgical mortality for anatomic hemispherectomy, primarily due to sparse data (SOE: Insufficient)
- Hydrocephalus requiring shunt placement after multilobar, unilobar, or focal resections is uncommon (SOE: Low)

Table 12. Strength of evidence for Key Question 3

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Levetiracetam	Discontinuation due to AEs	7/101 in one study[32] 0/92 in another study[34] 0/50 in another study[33]	High	Direct	Consistent	Precise	None suspected	None	Low	AEs rarely cause discontinuation
Levetiracetam	Serious or severe AE	In one study,[32] 12/101 had a "serious" event but none were LEV-related. 32 had a "serious" event and 2/32 were LEV-related	High	Direct	Unknown	Precise	None suspected	None	Insufficient	NA
Levetiracetam	Non-severe bronchitis	10% (10/101)[32]	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA
Levetiracetam	Non-severe convulsion	10% (10/101)[32]	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA
Topiramate	Discontinuation due to AEs	3%-5% with placebo and all three dose groups of one RCT[69] 3 events total in 58 patients receiving one of 4 doses in the other RCT[68] 12% (5/41) in a nonrandomized comparative study[36]	Moderate	Direct	Consistent	Precise	None suspected	No dose-response association	Moderate	AEs rarely cause discontinuation

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Topiramate	Serious or severe AE	3%-5% with placebo and all three dose groups of one RCT[69] 3 events total in 58 patients receiving one of 4 doses in an RCT[68] 0% (9/41) in a nonrandomized comparative study[36]	Moderate	Direct	Consistent	Precise	None suspected	No dose-response association	Moderate	Severe AEs are rare
Topiramate	Loss of appetite	One RCT[69] found that risk increased with dose (5% placebo, 11% with 5-15 mg/kg/day, and 16% with 25 mg/kg/day) One RCT[68] found that risk increased with dose (7% with 3 mg/kg/day, 8% with 5-15 mg/kg/day, and 20% with 25 mg/kg/day) 2% (1/41) in a nonrandomized comparative study[36]	Moderate	Direct	Consistent	Precise	None suspected	Dose response association	Moderate	Loss of appetite is a risk

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Topiramate	Upper respiratory tract infection	One RCT[69] found that risk increased with dose (14% placebo, 21% with 5 mg/kg/day, and 22% with 15-25 mg/kg/day) One RCT[68] found that risk increased with dose (0% with 3 mg/kg/day, 8% with 5 mg/kg/day, 15% with 15 mg/kg/day, and 38% with 25 mg/kg/day)	Moderate	Direct	Consistent	Precise	None suspected	Dose response association	Moderate	Upper respiratory tract infection is a risk
Topiramate	Bronchitis	One RCT[68] found that risk increased with dose (0% with 3-5 mg/kg/day, 8% with 15 mg/kg/day, and 13% with 25 mg/kg/day) Another RCT[69] found no dose response association (0% placebo, 8% for 5 mg/kg/day, 3% for 15 mg/kg/day, and 8% for 25 mg/kg/day)	Moderate	Direct	Inconsistent on dose-response association	Precise	None suspected	None	Insufficient	NA

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Topiramate	Vomiting	One RCT[68] found that risk increased with dose (7% with 3 mg/kg/day, 8% with 5 mg/kg/day, 15% with 15 mg/kg/day, and 20% with 25 mg/kg/day) Another RCT[69] found no dose response association (5% placebo, 18% for 5 mg/kg/day, 8% for 15 mg/kg/day, and 16% for 25 mg/kg/day) One nonrandomized comparative study reported 2% (1/41)	Moderate	Direct	Inconsistent on dose-response association	Precise	None suspected	None	Insufficient	NA

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Topiramate	Weight decrease	One RCT[68] found that risk increased with dose (0% with 3-5-15 mg/kg/day, and 13% with 25 mg/kg/day) Another RCT found no dose response association (3% placebo, 0% for 5 mg/kg/day, 5% for 15 mg/kg/day, and 14% for 25 mg/kg/day)	Moderate	Direct	Inconsistent on dose-response association	Precise	None suspected	None	Insufficient	NA
Topiramate	Hypohydrosis	One pre/post study reported a rate of 48% (39/81) One nonrandomized comparative study reported a rate of anhidrosis of 2% (1/41)	High	Direct	Inconsistent	Precise	None suspected	None	Insufficient	NA

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Lamotrigine	Discontinuation due to AEs	A short-term RCT reported 0% discontinuations due to AEs in both groups (N=19 per group). During the long-term open label phase the rate was 9% (18/204)	Moderate	Direct	Unknown	Precise	None suspected	None	Low	AEs rarely cause discontinuation
Lamotrigine	Serious or severe AE	A short-term RCT reported 1/19 serious bronchitis and 1/19 status epilepticus. During the long-term open label phase, 8% had pneumonia (16/204), 6% (12/204) had status epilepticus, 6% (12/204) had complex partial seizures, 4% (12/204) had fever, 3% (6/204) had convulsion, 3% (6/204) had dehydration, and 3% (12/204) had gastroenteritis	Moderate	Direct	Unknown	Precise	None suspected	None	Low	Severe AEs are rare

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Lamotrigine	Non-serious events	In the long-term open label phase, the most common events were fever (45%, 92/204), upper respiratory tract infection (28%, 58/204), and ear infection (22%, 45/204)	High	Direct	Unknown	Precise	None suspected	None	Insufficient	NA
Phenytoin	Non-serious events	One pre/post study[39] reported that four events were experienced by at least 10% of infants: drowsiness 22% (12/55), gingival hyperplasia 15% (8/55), sleep troubles 15% (8/55), and hyperactivity: 11% (6/55)	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA
Vigabatrin	Withdrawal due to AEs	One pre/post study[31] reported that 9% (9/103) discontinued due to AEs	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Vigabatrin	Vision abnormalities	One pre/post study[31] reported that prior to vigabatrin, 69% (34/49) had vision abnormalities. During vigabatrin, 81% (50/62) had at least one abnormal exam. After vigabatrin, 63% (31/49) had vision abnormalities	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA
Rufinamide	Withdrawal due to AEs	One pre/post study[40] reported that 15% (15/103) discontinued due to AEs	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA
Rufinamide	Non-serious events	One pre/post study[39,40] reported that two events were experienced by at least 10% of infants: somnolence 12% (12/103), and irritability: 10% (10/103)	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Stiripentol	Any adverse events	One pre/post study[41] reported that 61% (58/103) had at least one adverse drug reaction	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA
Ketogenic diet	Withdrawal due to side effects or diet intolerance	Two studies: one found a rate of 2% (2/109) and another found a rate of 20% (2/10)	High	Direct	Inconsistent	Imprecise	None suspected	None	Insufficient	NA
Ketogenic diet	Constipation	Two studies: one found a rate of 32% (35/109)[46] and another found a rate of 20% (2/10)[42]	High	Direct	Consistent	Imprecise	None suspected	None	Insufficient	NA
Ketogenic diet	Vomiting	Two studies: one found a rate of 20% (22/109)[46] and another found a rate of 0% (0/10)[42]	High	Direct	Inconsistent	Imprecise	None suspected	None	Insufficient	NA
Ketogenic diet	Other specific side effects	Reported by single studies	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Modified Atkins Diet	Withdrawal due to side effects or diet intolerance	One study:[42] 13% (2/15) patients dropped out due to diet intolerance and had experienced "significant" weight loss.	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA
Modified Atkins Diet	Specific side effects	One study:[42] 27% vomiting (4/15), 13% constipation (2/15), 13% diarrhea (2/15), and 20% dysphagia (3/15)	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA
Anatomic Hemispherectomy	Surgical mortality	3 pre/post studies[58,62,71] (n=26) 0 of 2 children died,[71] 1 in 14 children died,[58] 0 of 10 died[62]	Low	Direct	Consistent	Imprecise	None suspected	None	Insufficient	NA

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Functional hemispherectomy/Hemispherotomy	Surgical Mortality	8 pre/post studies[50,52,54,55,58,62,71,72] (n=196)[a] 7 of 8 studies reported no deaths; 1 study (Kumar et al.)[54] reported 1 death (of 16 procedures); post-operatively the infant had refractory seizures and care was withdrawn	Low	Direct	Consistent	Precise	None suspected	None	Low	With functional hemispherectomy/hemispherotomy, surgical mortality is rare.
Multilobar/lobar/focal resection	Surgical Mortality	3 pre/post studies[62,71,72] (n=82) No deaths were reported.	Low	Direct	Consistent	Precise	None suspected	None	Low	With multilobar/lobar/focal resection, surgical mortality is rare.

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Multilobar/lobar/focal resection	Hydrocephalus	5 pre/post studies[52,62,71,72] 4 studies[52,62,71,72] (n=108)[b] reported no cases of post-operative hydrocephalus. 1 study[53] reported 3 cases after cortical resection (denominator unclear).	Low	Directness	Consistent	Precise	None suspected	None	Low	After multilobar, lobar, or focal resection, hydrocephalus requiring shunt placement is uncommon.

AE = Adverse effects; LEV = Levetiracetam; NA = not applicable; RCT = randomized controlled trial

[a] Nine infants appearing in Iwasaki et al. 2021[72] were already reported in Otsuki et al. 2013[50] (author correspondence); 196 represents the sum of hemispherectomy/hemispherotomy patients reported in these studies included for this report; Also, Roth et al.[62] included infants from 19 centers. For mortality, data for 7 patients cared for at 3 centers (University of California at Los Angeles, Cleveland Clinic, Great Ormond Street Hospital) may have been described in prior studies included in this report.[58,61,71] Thus, the number of unique patients represented for this outcome is 180 to 187.

[b]Roth et al.[62] included infants from 19 centers. For hydrocephalus, data from 1 patient cared for at Great Ormond Street Hospital may have appeared in a prior study.[71]

Discussion

Findings in Relation to the Decisional Dilemma

Overall, as anticipated, the evidence base for management of infantile epilepsies was sparse. We identified only six randomized controlled trials (RCTs), two non-randomized comparative studies, and 33 pre/post studies (mostly retrospective). In fact, for surgical interventions, despite only requiring studies to report outcome for 10 infants per procedure, we only identified 18 studies, and all 18 were retrospective pre/post studies. Given the difficult treatment decisions and high stakes faced by clinicians, families, and caregivers of infants with epilepsy, this limited evidence base represents an important evidence gap.

Effectiveness: Pharmacologic Interventions

Most infants with epilepsy receive a trial of pharmacologic interventions before other interventions including dietary or surgical treatments. However, our review found limited evidence for pharmacologic interventions (Key Question [KQ] 1). Although we included studies assessing 10 drugs (levetiracetam, topiramate, lamotrigine, phenytoin, vigabatrin, valproate, phenobarbital, carbamazepine, rufinamide, stiripentol) evidence was only sufficient to demonstrate effectiveness for a single drug, levetiracetam (strength of evidence [SOE]: Low).

For other medications, limitations of the evidence included a lack of control groups, concomitant medications, insufficient follow-up time, only a single study, and/or unreported critical outcomes. Regarding comparative effectiveness, freedom from monotherapy failure appears to be more likely with levetiracetam than phenobarbital (one study). Another study compared topiramate and carbamazepine, but its data were inconclusive. None of the studies measured the effectiveness of oxcarbazepine, even though it is one of the more commonly prescribed medications for age 0-36 months.[6]

Effectiveness: Dietary Interventions

Regarding dietary interventions, we found that for some infants, the ketogenic diet (KD) is effective for producing seizure freedom and reducing seizure frequency. The modified Atkins diet (MAD) also may reduces seizure frequency. Furthermore, the KD was more likely to reduce seizure frequency than the MAD (SOE: Low). Most studies of dietary interventions lacked control groups, were relatively small (e.g., pre/post studies ranged from 40 to 147 infants), and the two RCTs each enrolled less than 40 infants and had considerable inter-study variability in the specific foods and ratios indicated for a KD. Dietary therapy is often only considered for infants in whom multiple anti-seizure medications (ASM) have been unsuccessful. In two surveys, parents of children on the KD or about initiate the diet rated fewer seizures as their top priority (65-69%); however, need for fewer drugs and improved cognition were their next priorities.[14,73] Unfortunately, included studies failed to report on either of these outcomes.

Effectiveness: Surgical Interventions

For hemispherectomy/hemispherotomy, seizure freedom rates ranged from 7% to 76% at one year after surgery, although all studies except 1 reported rates higher than 50%.

In addition to the range of seizure rates, the heterogeneity of seizure etiologies, procedures and ancillary treatments, precluded conclusions regarding a quantitative estimate. Thus, we

concluded that surgery may cause seizure freedom in some infants (SOE: Low). These robust rates of seizure freedom reflect the fact that unlike ASMs, when successful, surgical interventions address the underlying cause of seizures.

We encountered similar variability across estimates of seizure frequency reduction. Although all studies found reductions in seizure frequency after surgery, the proportion of infants achieving one widely used definition of a favorable outcome (Engel I or II, ILAE I to IV, or >50% seizure reduction) ranged from 67% to 100% with most studies reporting outcomes at least one year. Due to this variability, along with important study limitations, evidence was insufficient to draw a conclusion regarding seizure frequency.

For infants undergoing other resections (frontal or temporal lobe resection, intralobar or multilobar resections, or posterior disconnection), rates of seizure freedom ranged from 40% to 70% over with follow up intervals from median 6 months to average 5.2 years (5 pre/post studies). Given study limitations and range of estimates, we concluded that other resections may cause seizure freedom in some infants (SOE: Low). Seizure reduction rates for these procedures was also variable, with 50% to 90% of infants achieving a favorable outcomes across variable endpoints (5 pre/post studies). Thus, evidence was insufficient to draw a conclusion regarding seizure reduction.

Parents may have particular concerns when considering surgical interventions. When asked about goals and priorities in considering epilepsy surgery for their child, parents of older children with epilepsy (age >36 months) rated seizure freedom as highest priority, followed by reduced medication, improved cognition, and greater independence.[15] One small qualitative study found that parents choosing surgery saw this choice as last option, but the only real chance at a normal life.[74] Although we only identified retrospective pre/post studies of surgical interventions, these studies do find that some infants achieve seizure freedom.

Harms

For the harms of treatment (KQ 3), detailed reporting only exists for studies of pharmacologic treatments. We concluded that for three medications (levetiracetam, topiramate, and lamotrigine), adverse effects are rarely severe enough to warrant discontinuation of the medication. Specifically for topiramate, we did find consistent evidence of dose-response effects for two non-severe adverse effects: loss of appetite and upper respiratory tract infection. Although parents worry about both short and long term adverse effects from drugs,[13] included studies only reported short-term harms and rarely measured neurodevelopmental outcomes. For diets, adverse effects were generally not reported.

Harms of dietary interventions were not well-reported, and evidence was insufficient to permit conclusions. Some parents may be concerned about dietary intolerance or the difficulty in maintaining special diets. We saw some suggestions of these problems in the evidence we reviewed, but not enough to draw clear conclusions.

We note that the long-term potential harms of pharmacological and dietary treatments remain unclear, since few studies followed patients for longer than one year. As many parents are understandably anxious to know about these long-term harms, particularly regarding neurocognitive development, long-term studies are particularly important for future work.

For surgical interventions, although studies reporting surgical mortality for functional hemispherectomy/hemispherotomy and multilobar, lobar, or focal resections reported rare rates (SOE: Low), adverse event reporting across studies was inconsistent, and evidence did not

permit estimates of the mortality risk. Inconsistent reporting across studies also precluded any quantitative estimates of rates of post-surgical adverse effects.

Regarding post-operative hydrocephalus, data were too sparse and patients too heterogenous to draw conclusions regarding development of hydrocephalus after hemispherectomy or hemispherotomy. Limited available data was consistent with other work[75] suggesting hydrocephalus may be more common after anatomic hemispherectomy (compared to functional hemispherectomy/hemispherotomy). Notably, nearly all studies reporting on hydrocephalus failed to report when it occurred. However, a study in older children found that post-operative hydrocephalus can occur up to 8.5 years after surgery.[75] Thus, rates of hydrocephalus may depend heavily on length of follow-up.

Evidence Gaps

We note several important evidence gaps. First, few studies have assessed treatments for children with epilepsies age <36 months. Despite lenient inclusion criteria (allowing less rigorous study designs, and including surgical studies with only 10 infants per treatment arm), we only identified a small evidence base. For example, although many different drugs and combinations of drugs are currently used in this population,[6] we only identified evidence for five drugs of which only levetiracetam had evidence sufficient to conclude effectiveness. Furthermore, many studies (particularly for surgical interventions) were only included because a subgroup analysis reported on infants meeting criteria. Such studies often did not report clinical information (i.e., baseline seizure frequency, concomitant treatments, seizure etiologies) for the subgroup of interest.

Second, studies primarily reported on seizure frequency and seizure freedom, but largely failed to describe other important outcomes such as hospitalization, neurodevelopment, infant quality of life, sleep outcomes, functional performance, and caregiver quality of life. In fact, only three studies described developmental outcomes (for surgical interventions) and only one study reported on functional assessment. This focus on seizure outcomes may be related to external pressures (i.e., focus on outcomes needed for drug approval) or perhaps ease of measurement. However, these outcomes are important to parents, caregivers and clinicians and reflect an important evidence gap.

Third, the most common study design in this literature was a single-arm study, and authors typically attributed outcomes (e.g., seizure freedom) to the study treatments alone, rather than other possible explanations (e.g., other treatments, spontaneous remission, short follow-up time). This attribution may be more reasonable for surgical studies (as compared to pharmacologic or dietary therapy studies) as these patients have typically failed pharmacologic and/or dietary treatments prior to undergoing surgery. However, in general, future clinical studies could benefit from greater awareness of alternative explanations of observed outcomes when considering trial designs.

Finally, we note the lack of evidence addressing several treatments including commonly used medications such as oxcarbazepine, as well as newer modalities including cannabidiol, neuromodulation and gene therapy. Our searches did identify pediatric studies of cannabidiol,[76-106] vagus nerve stimulation,[107-191] transcranial direct current stimulation,[192,193] and responsive neurostimulation,[194] but none met our inclusion criteria (typically these studies enrolled older children). Some studies of genetic testing or genome sequencing of children with epilepsy have been conducted,[195-203] and future work may elucidate whether such testing improves outcomes through the optimal selection of treatment. Some gene therapy trials may be published soon;

TSHA-105, which is an investigational gene therapy for a rare form of epilepsy called SLC13A5 deficiency, received European Union orphan drug status in August of 2021, and clinicaltrials.gov lists a trial begun in March of 2021 (https://clinicaltrials.gov/ct2/show/NCT04798235).

Strengths and Limitations

One strength of this review is the exhaustive search for any evidence for interventions in infants 1 month to <36 months. Given early concerns about potential for sparse or insufficient evidence, we considered several strategies and altered inclusion criteria to allow alternative study designs and smaller studies.[204] In addition, we removed a requirement that pre/post studies measure seizure frequency in the context of a prospective trial (i.e., not a chart review). This criterion was meant to address concerns about potential inconsistency and bias in seizure counts assessed outside the context of a formal study. However, had we used this criterion, nearly all surgical studies of effectiveness would have been excluded.

In addition, if abstracts only mentioned including children or pediatric populations, we screened the full text to ensure we captured any studies reporting data on age 1-36 months. We ultimately excluded over 1100 full articles that did not report any such data. However, these efforts identified 13 additional studies. Thus, almost a third of our evidence base (13 of 41 studies) could only have been identified with this level of scrutiny.

One limitation of this review is the exclusion of evidence published prior to 1999. Older studies may have assessed the efficacy in infants of some older ASM such as valproate, carbamazepine and phenytoin. Similarly, these criteria may have excluded older studies of procedures such as anatomic hemispherectomy or other procedures. However, including older studies would have raised potential challenges for applicability given changes in diagnosis and clinical care, and many of the newer ASM were not available earlier. Similarly, for surgical interventions, since some studies included patients extending back to the 1970's, changes in surgical technique and clinical care may limit generalizability of findings. Importantly, we note that the lack of included evidence on older medications and procedures does *not* mean clinicians should necessarily exclude these treatments from consideration when tailoring treatments for individual patients. Our report is intended to provide a rigorous assessment of all available evidence published during this time frame.

Our inclusion criteria for this review may be considered a strength or a limitation, depending on judgements about relevance. Any evidence review must strike a balance between including important/relevant studies and excluding misleading/irrelevant studies, but no objective threshold exists. Key inclusion criteria for this review involved patient age (at least 80% must have been age 1-36 months at the time of treatment) and study size ($n \geq 10$ for RCTs of any treatment, $n \geq 10$ for non-randomized studies of surgery, and $n \geq 30$ for non-randomized studies of medications or diets). Many have noted that this age group is clinically distinctive from both neonates and older children. Thus, some could argue our criteria were too lenient because we included studies that mixed this age group with others. Conversely, others might argue the criteria were too strict as some studies barely missed a numerical threshold (e.g., we excluded Arzimanoglou et al. (2019)[205] as only 68% of patients were age 1-36 months). Notably, our pre-protocol criteria were stricter: ≥ 85% age 1-36 months, and $n \geq 30$ for any study of medications or diet. During screening, we relaxed these criteria to include more studies we deemed sufficiently relevant, such as RCTs of medications or diets enrolling 11-29 infants.

Regarding etiology and seizure types, the scarcity and quality of evidence did not permit an examination of how these factors may influence treatment effectiveness. Seizure prognosis

depends heavily on underlying seizure syndrome and etiology, along with comorbidities and concurrent therapies (such as number of ASMs). However, studies reported these data inconsistently. In addition, medical care and diagnosis has significantly evolved over the time periods captured in these studies. These factors precluded summarizing evidence on any particular etiology or seizure type as well as quantitative synthesis.

In addition to the evidence gaps noted earlier, no studies reported data on the cost of treatments. From stakeholder interviews, we learned that the cost of the intervention was an important factor for parents of young patients. While the review may be helpful to guide clinicians on their decision making, it provides no information on this important factor.

Applicability

As we did not stratify seizure type or etiologies, there may be differences between the patient population within this review and the overall infantile epilepsy population. Certain etiologies (i.e., particular genetic causes) may not have been captured by this review as their specific conditions may not lead them to enroll in trials. Although the scope of our systematic review did not include infantile spasms, three studies[31,50,61] reported infants as having "epileptic spasms" which could include infantile spasms but also other seizure types of interest. Recent changes to nomenclature used to describe infantile spasms may have played a role.[9] One study by Jackson et al. (2017)[31] enrolled many patients with "epileptic spasms" which may have potentially been infantile spasms. We included these studies/infants, however, results may be less applicable depending on what proportion of study participants had infantile spasms.

We considered whether infants in included studies had similar baseline seizure frequency or seizure severity compared to infants with epilepsy in the general population. However, only 5 of 41 studies reported baseline seizure frequency,[38,40,54,61,206] and only 3 of 41 studies reported baseline seizure severity.[54,61,65] Thus, the evidence does not permit an assessment of applicability for either measure of disease severity.

A key issue with the applicability of the evidence on pharmacologic treatments concerns the use of concomitant medications. For pharmacotherapy, 11 of 15 studies enrolled infants who had already attempted other ASM, and they continued taking ASM even after the introduction of the medication under study. Studies reported many seizure types and syndromes, with few restrictions on enrollment, with one exception. The study by Grinspan et al. (2018)[29] only enrolled patients with nonsyndromic epilepsy, and thus its result do not apply to infants with epilepsy syndromes. Thus, most of the evidence applies to the addition of another ASM to an existing regimen for the treatment of any form of epilepsy. We also note that the study by Piña-Garza et al. (2008)[30,38] required a 40% response to lamotrigine in order for an infant to enter the randomized portion of the trial, and so its harms results only apply to lamotrigine responders.

Studies of dietary and surgical interventions are primarily relevant for infants with intractable epilepsy unresponsive to ASMs. As these interventions also require access to specialized expertise that is not widely available, not all infants and their families may have access. With regard to dietary studies, although studies often used the same Johns Hopkins protocol, differences in how the diet was implemented could affect applicability. For example, three studies[42,43,47] did not use an initial fasting period, with one study[48] switching from fasting to nonfasting in the middle of the study (perhaps because fasting is less feasible for this young population). In addition, studies aimed for different lipid to nonlipid ratios and had different diet schedules. Second, both KD and MAD require significant effort from parents, especially during the later stages when the patient transition from hospital to home. The considerable effort

required to maintain compliance with dietary protocol, may make them less feasible for certain families. Finally, among 8 studies, only one was conducted in the United States and one in Europe. The remaining five were conducted in Asia and Egypt. Different diets and ASM availability could influence infant diets and affect applicability of these dietary interventions.

For surgical interventions, most studies were single center studies, each likely reflecting outcomes from a small number of surgeons. In addition to potential differences in surgical techniques across surgeons, studies reported a range of variations which, in some cases, reflected developments in the field. The most notable of these was a shift away from anatomical hemispherectomy to functional hemispherectomy or hemispherotomy over time. Our review included studies reporting procedures performed over four decades (from 1979 to 2020). Given changes in surgical technique and clinical care, findings may be less applicable to infants undergoing surgery today. Finally, we included a study assessing surgery for infants with epilepsy due to tumor; however, care for these infants and their outcomes will differ in important ways from other infants undergoing surgical resection.

Implications for Clinical Practice, Education, Research, or Health Policy

Clinical Practice

This systematic review confirms the lack of high-quality evidence to support treatments of infantile epilepsies. For many interventions currently in use, particularly pharmacologic treatments, we identified no studies assessing efficacy in these age groups. Nevertheless, our findings do support the use of levetiracetam, KD, MAD, and surgical procedures such as hemispherectomy, hemispherotomy, and other resections as effective in some infants. For studies of dietary therapies and surgical treatments, nearly all infants enrolled had intractable epilepsies, reflecting the use of these treatments only after drug therapy has failed.

Research and Health Policy

The substantial evidence gaps we identified have important implications for future research. As noted above, for many medications in current use, no studies in this age group exist. Although medications in other clinical areas are often evaluated using placebo-controlled RCTs, we acknowledge some important challenges to performing such trials in this population. Given fears regarding the potential for brain injury with prolonged seizures, parents may be understandably reluctant to risk their child receiving placebo. Such considerations have led some clinicians to consider a placebo arm unethical. Creative approaches to trial design, such the withdrawal RCT included for KQ 1, may be necessary to address these issues. However, without randomization, inferring efficacy for drugs, dietary, and surgical therapies is likely to remain challenging given the number of concomitant therapies patients receive.

A key challenge we faced was the lack of full data reported separately for this age group. Many studies that likely included infants in this age range failed to report data for this subgroup separately, instead reporting outcomes for “pediatric” patients encompassing newborns to 18-year-olds. Interviews with key stakeholders suggested that neonates (age <1 month) also represent a clinically distinct group of patients. Thus, future studies should consider reporting data for these three subgroups (neonates, infants, older children) separately, to facilitate use of

these data. In addition, future studies should also report baseline seizure frequency, seizure severity, and prior treatments.

Evidence for surgical interventions was particularly weak, with no studies assessing different approaches and inconsistent reporting of many clinical variables and key information such as follow up duration which are critical for assessing outcomes and adverse effects. Performing a controlled trial for surgical interventions presents obvious challenges, both ethical and pragmatic. Researchers could directly compare a surgical intervention to another treatment, such as a third ASM, although concerns regarding whether such a comparison would be ethical might persist. Perhaps a more feasible next step for future trials would be designing a prospective multicenter observational cohort study. Such data could be captured by a multicenter registry with standardized measures (including developmental outcomes and reporting for adverse effects). A registry spanning large geographical areas and reporting observational data would offer other important advantages: 1) given the relatively small number of infants undergoing surgical interventions, gathering data across multiple centers would offer important improvements to detect efficacy and harms; 2) such a registry could facilitate consensus about how to measure outcomes and 3) provide a framework for prospectively collecting data. Existing consortiums could play a role in facilitating development.

Development of core outcomes specific to infants could also support these efforts. Important outcomes identified by key stakeholders during protocol development included seizure freedom, seizure frequency, seizure severity, Engel classification, all-cause mortality, hospitalization, neurodevelopmental outcomes, quality of life, sleep quality, caregiver quality of life, treatment cost, and other adverse events. Given the range of seizure etiologies and surgical interventions, future studies should not only report these outcomes, but report outcomes *separately* for different seizure etiologies (i.e., HME vs. focal cortical dysplasia) and surgeries (i.e.., focal cortical resection vs. frontal lobectomy). Without this level of detail, future systematic reviews are likely to encounter difficulty in drawing conclusions about specific etiologies or procedures.

Finally, as many seizure etiologies are relatively rare, families often face a challenge in identifying and then accessing a provider with clinical expertise. Furthermore, many infants with epilepsy also require other medical interventions, therapies, or services which may be challenging for families to obtain depending on their geographical proximity to specialized care or healthcare coverage. These and other factors may contribute to economic hardship after diagnosis.[207] However, using telehealth and expanding coverage could not only improve the number of families with access to specialized expertise, but facilitate larger clinical trials to assess efficacy and long term outcomes.

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Abbreviations

ASM – Anti-seizure medication
AHRQ – Agency for Healthcare Research and Quality
CI – Confidence interval
ILAE – International League Against Epilepsy
HME – Hemimegalencephaly
KD – Ketogenic diet
KI – Key Informant
KQ – Key Question
LEV – Levetiracetam
MAD – Modified Atkins diet
n – Number of studies
N – Number of patients
NA – Not applicable
NR – Not reported
PB – Phenobarbital
PICOTS – Patients, interventions, comparators, outcomes, timepoints, settings
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT – Randomized controlled trial
SC – Some concerns
SD – Standard deviation
SE – Standard error
SEAD – Supplemental Evidence And Data portal
SOE – Strength of evidence
SUDEP – Sudden unexpected death in epilepsy
TEP – Technical Expert Panel

Appendix A. Methods

Search Strategy

The search strategy was designed and conducted by an experienced Medical Research Librarian with input from the investigators. Another Librarian peer reviewed the search strategies using the PRESS Checklist. We applied the following limits and filters to the database searches:

- *Dates*. Our original EMBASE.com search (including Medline and EMBASE) covered January 1, 1999, to November 30, 2020. Our original PubMed search (for in-process and publisher supplied citations) covered August 1, 2020, to November 30, 2020. Periodic updates were run to capture new literature published since the date or the original searches, most recently on August 19, 2021.
- *Language*. Publications were excluded if they were written in a language other than English.
- *Publication status*. We searched for published studies and in-process and publisher-supplied citations.
- *Human or organism*. The search was limited to human subjects.
- *Study design*. No specific study design limits were applied.
- *Filters*. An exclusion filter was used to remove case reports, editorials, and conference materials, among other publication types.
- *Other restrictions*. Infants and children 3 years or younger.

We searched the following databases:

- Medline and EMBASE (via EMBASE.com) for published literature (January 1, 1999, to November 30, 2020) Original search: November 30, 2021; Updated August 19, 2021
- Medline (via PubMed) for in-process and publisher supplied citations (August 1, 2020, to November 30, 2020). Original search: November 30, 2020; Updated August 19, 2021

EMBASE.com Strategy: (Including Medline and EMBASE) 1/1/1999 – 11/30/2020 (updated 7/6/2021)—

1 'benign childhood epilepsy'/exp OR 'childhood absence epilepsy'/exp OR 'severe myoclonic epilepsy in infancy'/exp OR (dravet* NEXT/1 (disease OR syndrome))
2 ([infant]/lim OR [newborn]/lim OR 'newborn'/exp OR [preschool]/lim OR 'preschool child'/exp OR 'toddler'/exp OR babies:ab,ti,kw OR baby:ab,ti,kw OR child*:ti,ab,kw OR infan*:ab,ti,kw OR neonat*:ab,ti,kw OR newborn*:ab,ti,kw OR nicu:ab,ti,kw OR paediatric*:ab,ti,kw OR pediatric*:ab,ti,kw OR preschool*:ab,ti,kw OR toddler*:ab,ti,kw OR 'very young':ab,ti,kw OR (('younger than' OR under OR below) NEAR/3 (3 OR three)) OR ((3 OR three) NEAR/3 ('or below' OR 'or under' OR 'or younger'))) AND ('epilepsy'/exp OR 'epileptic patient'/exp OR epilep*:ti)
3 'infantile spasm'/exp OR (((infan* OR neonat* OR newborn*) NEAR/2 (convuls* OR seizure* OR spasm*)):ab,ti,kw)
4 ([infant]/lim OR [newborn]/lim OR 'newborn'/exp OR babies:ab,ti,kw OR baby:ab,ti,kw OR infan*:ab,ti,kw OR neonat*:ab,ti,kw OR newborn*:ab,ti,kw OR nicu:ab,ti,kw) AND ('febrile

convulsion'/exp OR 'seizure'/exp OR convuls*:ab,ti,kw OR spasm*:ab,ti,kw OR seizure*:ab,ti,kw)
5 acetazolamide OR acth OR 'adrenocorticotropic hormone' OR benzodiazepine* OR brivaracetam OR bromide OR cannabidiol OR carbamazepine OR clobazam OR clonazepam OR clorazepate OR corticotropin OR divalproex OR eslicarbazepine OR ethosuximide OR everolimus OR felbamate OR fenfluramine OR folate OR 'folic acid' OR frisium OR gabapentin OR lacosamide OR lamotrigine OR levetiracetam OR liposteroid OR lorazepam OR mesuximide OR methsuximide OR onfi OR oxcarbazepine OR perampanel OR phenobarbital OR phenytoin OR prednisone OR pregabalin OR primidone OR pyridoxine OR 'pyridoxal 5 phosphate' OR rufinamide OR sabril OR stiripentol OR thiopental OR thiopentone OR tiagabine OR topiramate OR valproate OR 'valproate semisodium' OR 'valproic acid' OR vigabatrin OR zonisamide
6 'ketogenic diet'/de OR keto*:ab,ti,kw OR ketogenic:ab,ti,kw OR 'low glycemic index':ab,ti,kw OR 'medium chain triglyceride':ab,ti,kw OR 'modified atkins':ab,ti,kw OR 'modified keto':ab,ti,kw OR 'modified ketogenic':ab,ti,kw
7 'craniotomy'/de OR 'hemispherectomy'/de OR 'laser surgery'/de OR 'lobectomy'/de OR 'corpus callosotomy' OR craniotom* OR (disconnect* NEAR/3 (hemispher* OR surg* OR procedure*)) OR hemispherecotom* OR hemispherotom* OR lesionectom* OR lobectom* OR (laser* NEAR/3 (ablat* OR operat* OR procedure* OR surg*)) OR (multilobar NEAR/3 disconnect*) OR (palliat* NEAR/3 operat*) OR procedure* OR surg* OR resect* OR resection OR transect* OR transection* OR 'sublobar resection' OR 'subpial transection'
8 'brain depth stimulation'/de OR 'brain responsive neurostimulator'/de OR 'deep brain stimulator'/de OR 'nerve stimulation'/de OR 'nerve stimulator'/de OR 'vagus nerve stimulation'/de OR 'brain stimulat*' OR 'deep brain stimulat*' OR 'electric brain stimulat*' OR 'external trigeminal nerve stimulat*' OR 'responsive brain stimulat*' OR 'responsive neurostimulat*' OR 'vagus nerve stimulat*' OR stimulation OR stimulator* OR ((brain OR 'deep brain' OR electric* OR responsive OR 'vagus nerve') NEAR/2 (electrostim* OR stimulat*)) OR neurostim*
9 'anhidrosis'/de OR 'adverse event'/de OR 'adverse drug reaction'/de OR 'behavior disorder'/de OR 'cognitive defect'/de OR 'developmental delay'/de OR 'developmental disorder'/de OR 'dystonia'/de OR 'liver injury'/de OR 'loss of appetite'/de OR 'motor dysfunction'/de OR 'organ damage'/de OR 'patient harm'/de OR 'sleep disorder'/de OR 'sweating'/de OR advers*:ab,ti,kw OR harm*:ab,ti,kw OR 'side effect':ab,ti,kw OR anhidrosis OR (appetite NEAR/3 (lose OR losing OR loss)) OR ((cognitiv* OR behavior* OR develop* OR motor OR movement OR neurodevelop*) NEAR/3 (effect* OR disorder* OR problem* OR symptom*)) OR ((cognitiv* OR develop* OR neurodevelopment*) NEAR/3 (delay* OR disorder* OR regress*)) OR dystonia OR hypohidrosis OR hypohydrosis OR (liver NEAR/3 (damag* OR injur*)) OR (miss* NEAR/3 milestone*) OR ((eat* OR perspir* OR sweat* OR sleep*) NEAR/3 (disorder* OR inability OR unable))
10 'parent'/de OR parent*:ab,ti,kw OR mother*:ab,ti,kw OR father*:ab,ti,kw
11 'treatment refusal'/de OR 'not treated':ab,ti,kw OR 'no treatment':ab,ti,kw OR untreat*:ab,ti,kw OR ((declin* OR forgo* OR 'not' OR no OR refus* OR withheld OR withhold*) NEXT/3 (treated OR treatment*))
12 [english]/lim AND [1999-2020]/py NOT ([animals]/lim NOT [humans]/lim OR abstract:nc OR annual:nc OR 'book'/de OR ((case NEXT/1 (report* OR stud*)):ti) OR 'case report'/de OR 'case study'/de OR conference:nc OR 'conference abstract':it OR 'conference paper'/de OR 'conference paper':it OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR diagnos*:ti OR 'diagnosis'/mj OR 'diagnostic accuracy'/mj OR 'diagnostic procedures'/mj OR

'diagnostic test'/mj OR 'diagnostic test accuracy study'/mj OR 'differential diagnosis'/mj OR 'editorial'/de OR editorial:it OR 'erratum'/de OR guideline*:ti OR letter:it OR 'note'/de OR note:it OR meeting:nc OR 'practice guideline'/de OR 'review'/exp OR sessions:nc OR 'short survey'/de OR symposium:nc OR animal*:ti OR experimental:ti OR (vitro:ti NOT vivo:ti) OR canine:ti OR dog:ti OR dogs:ti OR mouse:ti OR mice:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR swine:ti)
13 #1 OR #2 OR #3 OR #4
14 #13 AND #12 AND #5
15 #13 AND #12 AND (#6 OR #7 OR #8)
16 (#5 OR #6 OR #7 OR #8) AND #9 AND #12 AND #13
17 (#5 OR #6 OR #7 OR #8 OR #9) AND #10 AND #12 AND #13
18 #11 AND #12 AND #13
19 #14 OR #15 OR #16
20 #17 OR #18
21 #19 OR #20

PubMed Strategy: In-process and Publisher Supplied Citations 8/1/2020 – 11/30/2020 (updated 7/6/2021) —

1 "benign childhood epilepsy" OR "childhood absence epilepsy" OR "severe myoclonic epilepsy in infancy" OR dravet*[tiab]
2 (babies[ti] OR baby[ti] OR child*[ti] OR infan*[ti] OR neonat*[ti] OR newborn*[ti] OR nicu[ti] OR paediatric*[ti] OR pediatric*[ti] OR preschool*[ti] OR toddler*[ti] OR "very young"[ti] OR "younger than three"[tiab] OR "younger than 3"[tiab] OR "under three"[tiab] OR "under 3"[tiab] OR "below three"[tiab] OR "below 3"[tiab] OR "3 or below"[tiab] OR "3 or younger"[tiab] OR "three or below"[tiab] OR "three or younger"[tiab]) AND epilep*[ti]
3 "infantile spasm*" OR "neonatal seizure*" OR ((babies OR baby OR infan* OR neonat* OR newborn*) AND (convuls* OR seizure* OR spasm*))
4 acetazolamide OR acth OR "adrenocorticotropic hormone" OR benzodiazepine* OR brivaracetam OR bromide OR cannabidiol OR carbamazepine OR clobazam OR clonazepam OR clorazepate OR corticotropin OR divalproex OR eslicarbazepine OR ethosuximide OR everolimus OR felbamate OR fenfluramine OR folate OR "folic acid" OR frisium OR gabapentin OR lacosamide OR lamotrigine OR levetiracetam OR liposteroid OR lorazepam OR mesuximide OR methsuximide OR onfi OR oxcarbazepine OR perampanel OR phenobarbital OR phenytoin OR prednisone OR pregabalin OR primidone OR pyridoxine OR "pyridoxal 5 phosphate" OR rufinamide OR sabril OR stiripentol OR thiopental OR thiopentone OR tiagabine OR topiramate OR valproate OR "valproate semisodium" OR "valproic acid" OR vigabatrin OR zonisamide
5 "ketogenic diet" OR ketogenic OR "low glycemic index" OR "medium chain triglyceride" OR "modified atkins" OR "modified keto" OR "modified ketogenic"
6 "corpus callosotomy" OR craniotom* OR hemispherecotom* OR hemispherotom* OR laser*[ti] OR "laser surgery" OR lesionectom* OR lobectom* OR disconnect* OR resect* OR transect*
7 "brain stimulat*" OR "deep brain stimulat*" OR "electric brain stimulat*" OR "external trigeminal nerve stimulat*" OR "responsive brain stimulat*" OR "responsive neurostimulat*" OR "vagus nerve stimulat*" OR neurostim*

8 anhidrosis OR "adverse event*" OR "adverse drug reaction" OR "behavior disorder*" OR "cognitive defect*" OR "developmental delay*" OR "developmental disorder*" OR dystonia OR harm* OR "liver injur*" OR "loss of appetite" OR "motor dysfunction" OR "organ damage" OR "sleep disorder*" OR sweating OR "side effect*"
9 parent* OR mother* OR father*
10 "treatment refusal" OR "not treated" OR "no treatment" OR untreat* OR "decline treatment" OR "declined treatment" OR "forgo treatment" OR "refuse treatment" OR "refused treatment" OR "refusing treatment" OR "withheld treatment" OR "withhold treatment" OR "withholding treatment"
11 2020/08/01:2020/11/30[edat] AND (inprocess[sb] OR publisher [sb]) NOT (animal* OR case OR "case reports" OR comment OR editorial OR guideline* OR letter OR news OR "practice guideline" OR canine OR dog OR dogs OR mouse OR mice OR rabbit* OR rat OR rats OR rodent* OR sheep OR swine)
12 #1 OR #2 OR #3
13 #4 AND #11 AND #12
14 (#5 OR #6 OR #7) AND #11 AND #12
15 ((#4 OR #5 OR #6 OR #7) AND #8) AND #11 AND #12
16 ((#4 OR #5 OR #6 OR #7 OR #8) AND #9) AND #11 AND #12
17 #10 AND #11 AND #12
18 #13 OR #14 OR #15
19 #16 OR #17
20 #18 OR #19

EMBASE Field Searching Codes—

:ab = Abstract
:ti = Title
/de = EMTREE subject heading
/exp = Exploded EMTREE subject heading
:it = Publication type
:kw = Keyword
/lim = Limit by group
/mj = Major EMTREE subject heading
:nc = Conference name
NEAR/x = Near proximity operator
NEXT/x = Next proximity operator
/py = Publication year
* = Truncation/wildcard character

PubMed Field Searching Codes—

[ab] = Abstract
[edat] = Entry date
[sb] = Subset
[ti] = Title
* = Truncation/wildcard character

Inclusion Criteria

As suggested in the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Center (EPC) Methods Guide for Comparative Effectiveness Reviews, we list the inclusion criteria separately for several categories: publication type, study design, patient characteristics, intervention characteristics, setting, and outcome data.[1]

Publication Criteria

1. **Full-length articles.** The article must be published as a full-length, peer-reviewed study. We did not include abstracts or meeting presentations because they do not include sufficient details about experimental methods to permit an evaluation of study design and conduct; they may also contain only a subset of measured outcomes.[2,3] Additionally, it is not uncommon for abstracts that are published as part of conference proceedings to have inconsistencies compared with the final study publication or to describe studies that are never published as full articles.[4-7]
2. **Publication date.** We included studies published from 1999 to present. Earlier articles are unlikely to reflect current practice.
3. **Redundancy.** To avoid double-counting patients, when several reports of overlapping patients are available, we included outcome data only from the report with the most patients. We included data from a smaller publication when it reports data on an included outcome that was not provided by the largest report or reports longer followup data for an outcome.
4. **English language.** This review's compressed timeframe did not permit translation of non-English-language articles.

Study Design Criteria

1. We included only empirical studies; thus, we excluded reviews, letters, guidelines, position statements, and commentaries. We used systematic reviews only to identify empirical studies, as a supplement to the full literature search described in the section below titled Literature Search Strategy.
2. We excluded studies of diagnosis as well as studies of provider/organization interventions such as awareness campaigns.
3. For single-treatment effectiveness in Key Questions 1 and 2, we employed a staged approach. Specifically, we first required that studies must have two or more separate groups of patients, one of which received inactive treatment such as placebo or sham (in order to measure effectiveness). We did not require that patients be randomly assigned to groups, nor did we require that studies plan their comparison(s) prospectively. If no such controlled studies exist for a given treatmentfor a given treatment, we examined pre-post studies of that treatment.
4. For comparative effectiveness in Key Questions 1 and 2, we required that studies directly compare two or more management strategies.
5. For Key Question 3 (harms), we included single-arm studies as well as controlled studies.

6. To be included for any Key Question, the study must report outcome data on at least 30 patients in each group. We made exceptions for randomized trials and studies of surgical interventions, for which we required outcome data only on at least 10 patients per treatment.

Patient Criteria

1. At enrollment, infants (age 1 month to <36 months) must have a diagnosis of epilepsy. We did not require EEG confirmation of seizures for inclusion.
2. At enrollment, patients must not have had febrile seizures or infantile spasms or West sydrome as their primary diagnosis. We excluded patients being treated primarily for the following conditions at enrollment: nonepileptic seizures, metabolic seizures, or other seizures not due to epilepsy. In addition, as this review is intended to focus primarily on nonacute management of epilepsy, we excluded patients treated for status epilepticus. At least 80% of patients must have been experiencing seizure types of interest (e.g., partial seizures) at the time of treatment.
3. For the age of enrolled patients, we required either that 1) studies enroll a population for which at least 80% were age 1 month to <36 months) or 2) that studies report data specifically for this age group.

Intervention Criteria

1. Active interventions must have been one of specific treatments listed in the table below. We excluded studies that reported outcome data only for a heterogeneous set of treatments (e.g., different infants receiving different pharmacologic agents, infants undergoing different surgical procedures).
2. For dietary interventions (e.g., ketogenic diet), we required studies to report either confirmation of dietary components by the study administrator, or that parents were educated in advance about what the diet involves. Thus, we excluded studies of dietary interventions if the use of the diet was based solely on parent report.
3. For gene therapy, we included treatment for only the following conditions: Dravet syndrome, Angelman syndrome, and Rett syndrome.

Table A-1. Included interventions

Category	Interventions
Pharmacologic	Brivaracetam
	Cannabidiol
	Carbamazepine
	Clobazam
	Clonazepam
	Diazepam
	Divalproex
	Eslicarbazepine
	Ethosuximide
	Everolimus
	Felbamate

Category	Interventions
	Fenfluramine
	Gabapentin
	Lacosamide
	Lamotrigine
	Levetiracetam
	Oxcarbazepine
	Perampanel
	Phenobarbital
	Phenytoin
	Pregabalin
	Primidone
	Rufinamide
	Stiripentol
	Tiagabine
	Topiramate
	Valproate
	Vigabatrin
	Zonisamide
Dietary therapy	Ketogenic diet
	Modified Atkins
	Low glycemic index
	Modified ketogenic diet
	Medium-chain triglyceride diet
Surgery	Corpus callosotomy
	Laser ablation
	Hemispherectomy/ Hemispherotomy
	Multiple subpial transections
	Resective surgery
Neuromodulation stimulation	Vagus nerve stimulation
Gene therapy	Gene therapy only for Dravet syndrome, Angelman syndrome, or Rett syndrome

Setting Criteria

1. Any setting.

Data Criteria

1. The study must report data pertaining to one of the outcomes of interest (see outcome list below). The review team consulted the Core Outcomes Set for epilepsy when revising this outcome list.[8]

2. For effectiveness/comparative effectiveness, we included only studies with followup duration of 12 or more weeks. However, for harms data, we extracted data from all reported time points.

Outcomes

- All-cause mortality
- SUDEP
- Hospitalization
- Seizure freedom
- Seizure frequency
- Seizure severity (including seizure duration, seizure burden, and status epilepticus)
- Engel classification
- Progression to other seizure types or syndromes (e.g., infantile spasms, Lennox-Gastaut syndrome)
- Time to seizure remission
- Neurodevelopment
- Quality of life (including eating)
- Sleep outcomes (e.g., total time spent asleep at night)
- Behavioral function
- Cognitive function
- Functional performance (including school)
- Social function
- Caregiver anxiety
- Caregiver quality of life
- General health status
- Cost of treatment
- Adverse events (e.g., infection, new neurological deficits, surgical complications, irritability, somnolence, dizziness, drug toxicity)

Risk of Bias Assessment

We define risk of bias as the risk that a study's point estimate of the effect size is inaccurate. For any outcomes that received strength-of-evidence (SOE) grades, we assessed the risk of bias (which is one of several inputs to the SOE). We assessed randomized trials for Key Question 1 and 2 using the Cochrane Risk of Bias 2 (ROB2) tool. The domains of ROB2 are:

- Randomization process
- Deviations from intended interventions
- Missing outcome data
- Measurement of the outcome
- Selection of the reported result

For nonrandomized studies with control groups for Key Question 1 and 2, we used the Risk of Bias in Non-randomized Studies (ROBINS-I) tool. The domains of ROBINS-I are:

- Confounding
- Selection of participants into the study
- Classification of interventions
- Deviations from intended interventions

- Missing outcome data
- Measurement of the outcome
- Selection of the reported result

For studies without control groups, we followed EPC guidance and use the following nine items:

- Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
- Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
- Did the study maintain fidelity to the intervention protocol?
- If attrition (overall or differential nonresponse, dropout, loss to followup, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?
- Were the outcome assessors blinded to the intervention or exposure status of participants?
- Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?
- Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?
- Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?
- Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?

For outcomes receiving SOE grades, we used the items to categorize each outcome of each study as either Low, Moderate, or High risk of bias. This categorization was not be based on a numerical score, but rather was a subjective judgment based on the items assessed. Due to the subjectivity, two raters independently assessed each study's risk of bias, with disagreements resolved by discussion.

Appendix B. Excluded Studies

Table B-1. Studies excluded at full-text

Study	Reason for Exclusion
Aaberg et al. (20120)[9]	Less than 80% were ≥1 month to <36 months
Aalbers et al. (2012)[10]	Less than 80% were ≥1 month to <36 months
Abbaskhanian et al. (2012)[11]	Less than 80% were ≥1 month to <36 months
Abdel-Mannan et al. (2020)[12]	Data not specific to a treatment
Abdelmesih et al. (2021)[13]	Less than 80% were ≥1 month to <36 months
Abdelmoity et al. (2021)[14]	Less than 80% were ≥1 month to <36 months
Abdelmoity et al. (2021)[15]	Unclear if at least 80% were age 1-36 months at time of treatment
Abend et al. (2011)[16]	Neonates
Abraham et al. (2019)[17]	Less than 80% were ≥1 month to <36 months
Abuelem et al. (2013)[18]	Less than 80% were ≥1 month to <36 months
Aburahma et al. (2015)[19]	Less than 80% were ≥1 month to <36 months
Ackers et al. (2011)[20]	Less than 80% were ≥1 month to <36 months
Ag Sgüder et al. (2016)[21]	Seizure type outside the scope
Agostinelli et al. (2013)[22]	Less than 80% were ≥1 month to <36 months
Agrawal et al. (2009)[23]	Seizure type outside the scope
Aguirre-Velázquez et al. (2017)[24]	Parent, but not on their preferences
Akhondian et al. (2020)[25]	Less than 80% were ≥1 month to <36 months
Akiyama et al. (2011)[26]	Less than 80% were ≥1 ≥month to <36 months
Al Ajlouni et al. (2005)[27]	Less than 80% were ≥1 month to <36 months
Al-Baradie et al. (2021)[28]	Less than 80% were ≥1 month to <36 months
Al Khayat et al. (2010)[29]	Less than 80% were ≥1 month to <36 months
Albert et al. (2014)[30]	Less than 80% were ≥1 month to <36 months
Albsoul-Younes et al. (2004)[31]	Less than 80% were ≥1 month to <36 months
Aldenkamp et al. (2002)[32]	Less than 80% were ≥1 month to <36 months
Aldenkamp et al. (2016)[33]	Narrative review
AL-Eitan et al. (2019)[34]	No outcomes of interest
Alem et al. (2021)[35]	Less than 80% were ≥1 month to <36 months
Alexandre et al. (2006)[36]	Less than 80% were ≥1 month to <36 months
Alexiou et al. (2009)[37]	N<10 Surgery
Alexopoulos et al. (2005)[38]	Treatment to halt acute seizures (not prevention)
Alexopoulos et al. (2006)[39]	Less than 80% were ≥1 month to <36 months
Ali et al. (2012)[40]	No outcomes of interest
Ali et al. (2014)[41]	Less than 80% were ≥1 month to <36 months
Ali et al. (2017)[42]	Less than 80% were ≥1 month to <36 months
Alireza et al. (2010)[43]	Less than 80% were ≥1 month to <36 months
Aljabri et al. (2008)[44]	Not a treatment of interest
Alkonyi et al. (2011)[45]	Not a treatment of interest
Alkonyi et al. (2011)[46]	Less than 80% were ≥1 month to <36 months
Almeida et al. (2008)[47]	Less than 80% were ≥1 month to <36 months
Alomar et al. (2018)[48]	Less than 80% were ≥1 month to <36 months
Alper et al. (2017)[49]	Comment/guideline/position statement/editorial
Alqahtani et al. (2016)[50]	Parent, but not on their preferences
Alshafai et al. (2014)[51]	Less than 80% were ≥1 month to <36 months
Altunbasa¸et al. (2001)[52]	Less than 80% were ≥1 month to <36 months
Al-Twaijri et al. (2002)[53]	Less than 80% were ≥1 month to <36 months
Amari et al. (2015)[54]	Less than 80% were ≥1 month to <36 months
Amirsalari et al. (2011)[55]	No outcomes of interest
Anderson et al. (2015)[56]	Less than 80% were ≥1 month to <36 months
Annegers et al. (2000)[57]	Age at treatment not reported
Appavu et al. (2016)[58]	Treatment to halt acute seizures (not prevention)
Appleton et al. (2003)[59]	Treatment to halt acute seizures (not prevention)
Appleton et al. (2015)[60]	Comment/guideline/position statement/editorial
Araki et al. (2006)[61]	Less than 80% were ≥1 month to <36 months
Arévalo-Astrada et al. (2021)[62]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Arhan et al. (2009)[63]	Less than 80% were ≥1 month to <36 months
Arhan et al. (2010)[64]	Less than 80% were ≥1 month to <36 months
Arhan et al. (2011)[65]	No outcomes of interest
Arican et al. (2020)[66]	Neonates
Arifin et al. (2020)[67]	Case report (N=3 or less)
Armijo et al. (1999)[68]	Less than 80% were ≥1 month to <36 months
Armutcu et al. (2004)[69]	Less than 80% were ≥1 month to <36 months
Arslan et al. (2016)[70]	Less than 80% were ≥1 month to <36 months
Arts et al. (2004)[71]	Doesn't report specific intervention
Arts et al. (2019)[72]	Less than 80% were ≥1 month to <36 months
Arya et al. (2014)[73]	Less than 80% were ≥1 month to <36 months
Arya et al. (2015)[74]	Less than 80% were ≥1 month to <36 months
Arya et al. (2018)[75]	Seizure type outside the scope (E.g., West syndrome, infantile spasms)
Arzimanoglou et al. (2000)[76]	N<10 Surgery
Arzimanoglou et al. (2019)[77]	Less than 80% were ≥1 month to <36 months
Asadi-Pooya et al. (2005)[78]	Less than 80% were ≥1 month to <36 months
Asadi-Pooya et al. (2013)[79]	Less than 80% were ≥1 month to <36 months
Asano et al. (2007)[80]	Case report (N=3 or less)
Asano et al. (2009)[81]	Less than 80% were ≥1 month to <36 months
Ashrafi et al. (2010)[82]	No outcomes of interest
Ashrafi et al. (2010)[83]	No outcomes of interest
Ashrafi et al. (2017)[84]	N of 4-29 non-surgery
Ashrafi et al. (2018)[85]	Less than 80% were ≥1 month to <36 months
Ates et al. (2006)[86]	Data not specific to a treatment
Attilakos et al. (2006)[87]	Less than 80% were ≥1 month to <36 months
Attilakos et al. (2007)[88]	Less than 80% were ≥1 month to <36 months
Attilakos et al. (2007)[89]	Less than 80% were ≥1 month to <36 months
Attilakos et al. (2009)[90]	Less than 80% were ≥1 month to <36 months
Attilakos et al. (2018)[91]	Less than 80% were ≥1 month to <36 months
Attilakos et al. (2019)[92]	Less than 80% were ≥1 month to <36 months
Aungaroon et al. (2017)[93]	Less than 80% were ≥1 month to <36 months
Auvichayapat et al. (2013)[94]	Less than 80% were ≥1 month to <36 months
Auvichayapat et al. (2016)[95]	Not a treatment of interest
Awaad et al. (2005)[96]	N of 4-29 nonsurgery
Aycicek et al. (2007)[97]	Less than 80% were ≥1 month to <36 months
Aydin et al. (2005)[98]	Less than 80% were ≥1 month to <36 months
Azevedo et al. (2017)[99]	Less than 80% were ≥1 month to <36 months
Babayigit et al. (2006)[100]	Less than 80% were ≥1 month to <36 months
Baby et al. (2018)[101]	Less than 80% were ≥1 month to <36 months
Baca et al. (2013)[102]	Less than 80% were ≥1 month to <36 months
Bach et al. (2020)[103]	Less than 80% were ≥1 month to <36 months
Bajer et al. (2020)[104]	Less than 80% were ≥1 month to <36 months
Baker et al. (2005)[105]	Less than 80% were ≥1 month to <36 months
Bakhshandeh Bali et al. (2013)[106]	Less than 80% were ≥1 month to <36 months
Bakke et al. (2011)[107]	Less than 80% were ≥1 month to <36 months
Bali et al. (2013)[108]	Less than 80% were ≥1 month to <36 months
Bali et al. (2014)[109]	Less than 80% were ≥1 month to <36 months
Bandyopadhyay et al. (2003)[110]	Less than 80% were ≥1 month to <36 months
Banerjea et al. (2002)[111]	Less than 80% were ≥1 month to <36 months
Bansal et al. (2013)[112]	Less than 80% were ≥1 month to <36 months
Bansal et al. (2014)[113]	N of 4-29 non-surgery
Bansal et al. (2017)[114]	Less than 80% were ≥1 month to <36 months
Banu et al. (2007)[115]	Less than 80% were ≥1 month to <36 months
Banu et al. (2012)[116]	No outcomes of interest
Bao et al. (2011)[117]	Less than 80% were ≥1 month to <36 months
Barba et al. (2021)[118]	Less than 80% were ≥1 month to <36 months
Barcia-Salorio et al. (1999)[119]	Narrative review
Barik et al. (2014)[120]	N of 4-29 non-surgery

Study	Reason for Exclusion
Barone et al. (2003)[121]	Narrative review
Barron et al. (2000)[122]	Less than 80% were ≥1 month to <36 months
Barwick et al. (2017)[123]	Less than 80% were ≥1 month to <36 months
Barzegar et al. (2010)[124]	Less than 80% were ≥1 month to <36 months
Basheer et al. (2007)[125]	Less than 80% were ≥1 month to <36 months
Battaglia et al. (1999)[126]	N<10 Surgery
Battaglia et al. (2006)[127]	Patients overlapped with another included publication.[128]
Battaglia et al. (2016)[129]	N of 4-29 non-surgery
Battino et al. (2001)[130]	Less than 80% were ≥1 month to <36 months
Baudou et al. (2019)[131]	Neonates
Bauman et al. (2005)[132]	Case report (N=3 or less)
Baumer et al. (2018)[133]	Narrative review
Bawden et al. (1999)[134]	Less than 80% were ≥1 month to <36 months
Beaton et al. (2012)[135]	Less than 80% were ≥1 month to <36 months
Beghi et al. (2003)[136]	Less than 80% were ≥1 month to <36 months
Belohlavkova et al. (2019)[137]	Less than 80% were ≥1 month to <36 months
Beltrán-Sarmiento et al. (2018)[138]	Less than 80% were ≥1 month to <36 months
Beniczky et al. (2010)[139]	Less than 80% were ≥1 month to <36 months
Benifla et al. (2006)[140]	Less than 80% were ≥1 month to <36 months
Benifla et al. (2006)[141]	Less than 80% were ≥1 month to <36 months
Benifla et al. (2008)[142]	Less than 80% were ≥1 month to <36 months
Benifla et al. (2009)[143]	Case report (N=3 or less)
Benova et al. (2019)[144]	Less than 80% were ≥1 month to <36 months
Ben-Zeev et al. (2003)[145]	Less than 80% were ≥1 month to <36 months
Berg et al. (2003)[146]	Less than 80% were ≥1 month to <36 months
Berg et al. (2006)[147]	Less than 80% were ≥1 month to <36 months
Berg et al. (2009)[148]	Less than 80% were ≥1 month to <36 months
Berg et al. (2009)[149]	Likely <80% in right age group; also specific intervention not provided
Berg et al. (2014)[150]	Less than 80% were ≥1 month to <36 months
Bergmann et al. (2020)[151]	Simulations
Bergqvist et al. (2005)[152]	Less than 80% were ≥1 month to <36 months
Bermeo-Ovalle et al. (2016)[153]	Comment/guideline/position statement/editorial
Bernardino et al. (2016)[154]	Less than 80% were ≥1 month to <36 months
Berry-Kravis et al. (2001)[155]	Less than 80% were ≥1 month to <36 months
Bertsche et al. (2014)[156]	Less than 80% were ≥1 month to <36 months
Beume et al. (2010)[157]	Less than 80% were ≥1 month to <36 months
Bhatia et al. (2013)[158]	Case report (N=3 or less)
Bien et al. (2009)[159]	Less than 80% were ≥1 month to <36 months
Bird et al. (2011)[160]	Less than 80% were ≥1 month to <36 months
Biró et al. (2015)[161]	Less than 80% were ≥1 month to <36 months
Bittar et al. (2002)[162]	N<10 Surgery
Bjellvi et al. (2015)[163]	Data not specific to a treatment
Bjellvi et al. (2020)[164]	Data not specific to a treatment
Bjørnæs et al. (2013)[165]	Seizure type outside the scope (E.g., West syndrome, infantile spasms)
Bjurulf et al. (2020)[166]	Less than 80% were ≥1 month to <36 months
Blount et al. (2004)[167]	Less than 80% were ≥1 month to <36 months
Blount et al. (2006)[168]	Case report (N=3 or less)
Bodin et al. (2016)[169]	Less than 80% were ≥1 month to <36 months
Boerwinkle et al. (2018)[170]	Less than 80% were ≥1 month to <36 months
Bombardieri et al. (2010)[171]	N of 4-29 nonsurgery
Boon et al. (1999)[172]	Less than 80% were ≥1 month to <36 months
Borggraefe et al. (2013)[173]	Less than 80% were ≥1 month to <36 months
Borlot et al. (2020)[174]	N of 4-29 non-surgery
Boshuisen et al. (2009)[175]	Less than 80% were ≥1 month to <36 months
Boshuisen et al. (2010)[176]	Less than 80% were ≥1 month to <36 months
Boshuisen et al. (2012)[177]	Less than 80% were ≥1 month to <36 months
Boshuisen et al. (2014)[178]	Age at treatment not reported
Bosnyák et al. (2016)[179]	No intervention (just describes patients)

Study	Reason for Exclusion
Bosson et al. (2014)[180]	Didnt report how many had epilepsy when treated
Bostancioglu et al. (2009)[181]	Less than 80% were ≥1 month to <36 months
Bourgeois et al. (1999)[182]	Less than 80% were ≥1 month to <36 months
Bourgeois et al. (2000)[183]	Comment/guideline/position statement/editorial
Bourgeois et al. (2007)[184]	Less than 80% were ≥1 month to <36 months
Bouthillier et al. (2020)[185]	Less than 80% were ≥1 month to <36 months
Bower et al. (2015)[186]	Less than 80% were ≥1 month to <36 months
Boylan et al. (2002)[187]	Neonates
Boylan et al. (2004)[188]	Neonates
Braams et al. (2015)[189]	Out of scope
Braams et al. (2018)[190]	Less than 80% were ≥1 month to <36 months
Braams et al. (2019)[191]	Less than 80% were ≥1 month to <36 months
Brahimaj et al. (2014)[192]	Less than 80% were ≥1 month to <36 months
Brandl et al. (2010)[193]	Less than 80% were ≥1 month to <36 months
Brodbeck et al. (2006)[194]	Less than 80% were ≥1 month to <36 months
Brorson et al. (2019)[195]	Out of scope
Bujarski et al. (2013)[196]	Less than 80% were ≥1 month to <36 months
Buoni et al. (1999)[197]	Less than 80% were ≥1 month to <36 months
Burns et al. (2018)[198]	Less than 80% were ≥1 month to <36 months
Çaksen et al. (2002)[199]	Less than 80% were ≥1 month to <36 months
Çaksen et al. (2002)[200]	Less than 80% were ≥1 month to <36 months
Callenbach et al. (2009)[201]	Less than 80% were ≥1 month to <36 months
Camfield et al. (2001)[202]	Validation of QOL scale
Camp et al. (2015)[203]	Less than 80% were ≥1 month to <36 months
Camposano et al. (2008)[204]	Less than 80% were ≥1 month to <36 months
Cansu et al. (2006)[205]	Less than 80% were ≥1 month to <36 months
Cansu et al. (2008)[206]	Less than 80% were ≥1 month to <36 months
Cansu et al. (2012)[207]	Less than 80% were ≥1 month to <36 months
Capovilla et al. (1999)[208]	N of 4-29 non-surgery
Caraballo et al. (2005)[209]	Less than 80% were ≥1 month to <36 months
Caraballo et al. (2006)[210]	Less than 80% were ≥1 month to <36 months
Caraballo et al. (2006)[211]	Less than 80% were ≥1 month to <36 months
Caraballo et al. (2011)[212]	N<10 surgery
Caraballo et al. (2011)[213]	Less than 80% were ≥1 month to <36 months
Caraballo et al. (2011)[214]	Less than 80% were ≥1 month to <36 months
Caraballo et al. (2013)[215]	Less than 80% were ≥1 month to <36 months
Caraballo et al. (2014)[216]	Less than 80% were ≥1 month to <36 months
Caraballo et al. (2014)[217]	Case report (N=3 or fewer)
Caraballo et al. (2014)[218]	Data not specific to a treatment
Caraballo et al. (2020)[219]	Less than 80% were ≥1 month to <36 months
Carpay et al. (2002)[220]	Less than 80% were ≥1 month to <36 months
Caruso et al. (2021)[221]	Less than 80% were ≥1 month to <36 months
Carvalho et al. (2018)[222]	Out of scope
Casas-Fernández et al. (2012)[223]	Less than 80% were ≥1 month to <36 months
Castro-Gago et al. (2006)[224]	Less than 80% were ≥1 month to <36 months
Catchpool et al. (2019)[225]	Less than 80% were ≥1 month to <36 months
Cats et al. (2007)[226]	Less than 80% were ≥1 month to <36 months
Cayir et al. (2014)[227]	No outcomes of interest
Cazali et al. (2003)[228]	Age at treatment not reported
Cengiz et al. (2000)[229]	Less than 80% were ≥1 month to <36 months
Cepeda et al. (1999)[230]	No outcomes of interest
Cepeda et al. (2020)[231]	Less than 80% were ≥1 month to <36 months
Cersósimo et al. (2011)[232]	Less than 80% were ≥1 month to <36 months
Cersósimo et al. (2011)[233]	Less than 80% were ≥1 month to <36 months
Chan et al. (2002)[234]	Not a treatment of interest
Chang et al. (2011)[235]	Less than 80% were ≥1 month to <36 months
Chang et al. (2020)[236]	N of 4-29 nonsurgery
Chapman et al. (2003)[237]	Not a full paper (abstract only)

Study	Reason for Exclusion
Chapman et al. (2005)[238]	Less than 80% were ≥1 month to <36 months
Chaudhuri et al. (2017)[239]	Less than 80% were ≥1 month to <36 months
Chen et al. (1999)[240]	Less than 80% were ≥1 month to <36 months
Chen et al. (2001)[241]	Less than 80% were ≥1 month to <36 months
Chen et al. (2002)[242]	No intervention (just describes patients)
Chen et al. (2006)[243]	Less than 80% were ≥1 month to <36 months
Chen et al. (2007)[244]	Case report (N=3 or fewer)
Chen et al. (2012)[245]	Less than 80% were ≥1 month to <36 months
Chen et al. (2014)[246]	Seizure type outside the scope (E.g., West syndrome, infantile spasms)
Chen et al. (2014)[247]	Less than 80% were ≥1 month to <36 months
Chen et al. (2015)[248]	Treatment to halt acute seizures (not prevention)
Chen et al. (2016)[249]	Less than 80% were ≥1 month to <36 months
Chen et al. (2018)[250]	Less than 80% were ≥1 month to <36 months
Chen et al. (2019)[251]	Less than 80% were ≥1 month to <36 months
Chhun et al. (2011)[252]	Less than 80% were ≥1 month to <36 months
Chieffo et al. (2011)[253]	Less than 80% were ≥1 month to <36 months
Chipaux et al. (2017)[254]	Less than 80% were ≥1 month to <36 months
Chipaux et al. (2019)[255]	Less than 80% were ≥1 month to <36 months
Chiron et al. (2000)[256]	Less than 80% were ≥1 month to <36 months
Chiron et al. (2006)[257]	Less than 80% were ≥1 month to <36 months
Choi et al. (2018)[258]	Less than 80% were ≥1 month to <36 months
Choi et al. (2019)[259]	Less than 80% were ≥1 month to <36 months
Chomtho et al. (2016)[260]	Less than 80% were ≥1 month to <36 months
Chugani et al. (2014)[261]	Less than 80% were ≥1 month to <36 months
Chugani et al. (2015)[262]	Less than 80% were ≥1 month to <36 months
Chung et al. (2014)[263]	Narrative review
Chu-Shore et al. (2010)[264]	No intervention (just describes patients)
Cilio et al. (2001)[265]	Less than 80% were ≥1 month to <36 months
Clusmann et al. (2004)[266]	Less than 80% were ≥1 month to <36 months
Clusmann et al. (2004)[267]	Less than 80% were ≥1 month to <36 months
Cnaan et al. (2017)[268]	Less than 80% were ≥1 month to <36 months
Cohen et al. (2019)[269]	Less than 80% were ≥1 month to <36 months
Cohen et al. (2020)[270]	Less than 80% were ≥1 month to <36 months
Colicchio et al. (2010)[271]	Less than 80% were ≥1 month to <36 months
Colicchio et al. (2012)[272]	Less than 80% were ≥1 month to <36 months
Connolly et al. (2020)[273]	Less than 80% were ≥1 month to <36 months
Conry et al. (2008)[274]	Less than 80% were ≥1 month to <36 months
Consales et al. (2013)[275]	Unable to obtain
Contin et al. (1999)[276]	Less than 80% were ≥1 month to <36 months
Conway et al. (2018)[277]	Less than 80% were ≥1 month to <36 months
Coppola et al. (2002)[278]	Less than 80% were ≥1 month to <36 months
Coppola et al. (2010)[279]	N of 4-29 nonsurgery
Cormack et al. (2007)[280]	Less than 80% were ≥1 month to <36 months
Cossu et al. (2008)[281]	Less than 80% were ≥1 month to <36 months
Cossu et al. (2013)[282]	Less than 80% were ≥1 month to <36 months
Cramer et al. (2014)[283]	Less than 80% were ≥1 month to <36 months
Crevier-Sorbo et al. (2020)[284]	Less than 80% were ≥1 month to <36 months
Cross et al. (2002)[285]	Less than 80% were ≥1 month to <36 months
Cross et al. (2014)[286]	Less than 80% were ≥1 month to <36 months
Çubukçu et al. (2018)[287]	Less than 80% were ≥1 month to <36 months
Cukiert et al. (2013)[288]	Less than 80% were ≥1 month to <36 months
Cukiert et al. (2013)[289]	Less than 80% were ≥1 month to <36 months
Curatolo et al. (2018)[290]	Less than 80% were ≥1 month to <36 months
Curry et al. (2012)[291]	Less than 80% were ≥1 month to <36 months
Curtiss et al. (2001)[292]	Cohort already reported on in 2 other papers;[293,294] this study does NR any additional outcomes of interest (SLR only reported post-op)
Cusmai et al. (2011)[295]	N of 4-29 nonsurgery
Czornyj et al. (2018)[296]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Da Silveira et al. (2006)[297]	N of 4-29 non-surgery
Dahlin et al. (2000)[298]	N of 4-29 non-surgery
Dahlin et al. (2004)[299]	Less than 80% were ≥1 month to <36 months
Dahlin et al. (2007)[300]	N of 4-29 non-surgery
Dahlin et al. (2012)[301]	N of 4-29 non-surgery
Dahlin et al. (2012)[302]	Less than 80% were ≥1 month to <36 months
Danguecan et al. (2017)[303]	No intervention (just describes patients)
Danguecan et al. (2019)[304]	Less than 80% were ≥1 month to <36 months
Danielsson et al. (2002)[305]	Less than 80% were ≥1 month to <36 months
Danielsson et al. (2009)[306]	Less than 80% were ≥1 month to <36 months
D'Argenzio et al. (2011)[307]	Less than 80% were ≥1 month to <36 months
Daszkiewicz et al. (2018)[308]	Less than 80% were ≥1 month to <36 months
Datta et al. (2000)[309]	No intervention (just describes patients)
Datta et al. (2006)[310]	Less than 80% were ≥1 month to <36 months
Datta et al. (2011)[311]	Less than 80% were ≥1 month to <36 months
Datta et al. (2017)[312]	Less than 80% were ≥1 month to <36 months
de Araujo et al. (2006)[313]	Less than 80% were ≥1 month to <36 months
de Brito et al. (2017)[314]	Less than 80% were ≥1 month to <36 months
de Kinderen et al. (2011)[315]	Protocol
de Kinderen et al. (2016)[316]	Less than 80% were ≥1 month to <36 months
de Knegt et al. (2020)[317]	Less than 80% were ≥1 month to <36 months
de Lange et al. (2018)[318]	Less than 80% were ≥1 month to <36 months
de Palma et al. (2020)[319]	Less than 80% were ≥1 month to <36 months
Dekker et al. (2010)[320]	Less than 80% were ≥1 month to <36 months
Delalande et al. (2003)[321]	Less than 80% were ≥1 month to <36 months
Deonna et al. (2000)[322]	Less than 80% were ≥1 month to <36 months
Desai et al. (2011)[323]	Less than 80% were ≥1 month to <36 months
Devinsky et al. (2016)[324]	Less than 80% were ≥1 month to <36 months
Devinsky et al. (2017)[325]	Less than 80% were ≥1 month to <36 months
Devinsky et al. (2019)[326]	Less than 80% were ≥1 month to <36 months
Devlin et al. (2003)[327]	Less than 80% were ≥1 month to <36 months
Di Bonaventura et al. (2005)[328]	Less than 80% were ≥1 month to <36 months
Di Gennaro et al. (2013)[329]	Less than 80% were ≥1 month to <36 months
Di Rocco et al. (2000)[330]	N<10 surgery
Diler Durgut et al. (2019)[331]	Less than 80% were ≥1 month to <36 months
DiMario et al. (2002)[332]	Less than 80% were ≥1 month to <36 months
Ding et al. (2011)[333]	Less than 80% were ≥1 month to <36 months
Ding et al. (2016)[334]	Less than 80% were ≥1 month to <36 months
Ding et al. (2018)[335]	Less than 80% were ≥1 month to <36 months
Dinopoulos et al. (2014)[336]	Less than 80% were ≥1 month to <36 months
Dlugos et al. (2001)[337]	Less than 80% were ≥1 month to <36 months
Dlugos et al. (2004)[338]	Age at treatment not reported
Dobre et al. (2015)[339]	Less than 80% were ≥1 month to <36 months
Doege et al. (2013)[340]	Less than 80% were ≥1 month to <36 months
Doeser et al. (2015)[341]	No outcomes of interest
Doksöz et al. (2015)[342]	Less than 80% were ≥1 month to <36 months
Domínguez-Carral et al. (2014)[343]	Not in English
Dong et al. (2004)[344]	Less than 80% were ≥1 month to <36 months
Donner et al. (2001)[345]	Case report (N=3 or fewer)
Doo et al. (2018)[346]	Less than 80% were ≥1 month to <36 months
Dooley et al. (1999)[347]	Less than 80% were ≥1 month to <36 months
Dorfer et al. (2013)[348]	N<10 surgery
D'Orio et al. (2019)[349]	Less than 80% were ≥1 month to <36 months
Dressler et al. (2010)[350]	Less than 80% were ≥1 month to <36 months
Dressler et al. (2015)[351]	Less than 80% were ≥1 month to <36 months
Dressler et al. (2018)[352]	N of 4-29 nonsurgery
Dressler et al. (2020)[353]	Less than 80% were ≥1 month to <36 months
Dressler et al. (2020)[354]	Patients overlapped with another included publication[355]

Study	Reason for Exclusion
Du et al. (2018)[356]	N<10, surgery
Du et al. (2019)[357]	Less than 80% were ≥1 month to <36 months
Duchowny et al. (1999)[358]	Less than 80% were ≥1 month to <36 months
Duchowny et al. (2002)[359]	Less than 80% were ≥1 month to <36 months
Dunlea et al. (2010)[360]	Less than 80% were ≥1 month to <36 months
Dureau-Pournin et al. (2014)[361]	Less than 80% were ≥1 month to <36 months
Dwivedi et al. (2017)[362]	Less than 80% were ≥1 month to <36 months
Ecevit et al. (2004)[363]	Less than 80% were ≥1 month to <36 months
Edelvik et al. (2013)[364]	Less than 80% were ≥1 month to <36 months
Egunsola et al. (2018)[365]	Less than 80% were ≥1 month to <36 months
Eid et al. (2020)[366]	Less than 80% were ≥1 month to <36 months
Eirís et al. (2000)[367]	Less than 80% were ≥1 month to <36 months
Eirís-Puñal et al. (1999)[368]	Less than 80% were ≥1 month to <36 months
Ekici et al. (2012)[369]	Less than 80% were ≥1 month to <36 months
El Mously et al. (2018)[370]	Less than 80% were ≥1 month to <36 months
Eldeen et al. (2012)[371]	No outcomes of interest
El-Ebiary et al. (2013)[372]	Less than 80% were ≥1 month to <36 months
Elliott et al. (2008)[373]	Less than 80% were ≥1 month to <36 months
Elliott et al. (2011)[374]	Less than 80% were ≥1 month to <36 months
Elliott et al. (2012)[375]	Less than 80% were ≥1 month to <36 months
Elliott et al. (2018)[376]	Age at treatment not reported
El-Rashidy et al. (2015)[377]	Less than 80% were ≥1 month to <36 months
Elsayed et al. (2016)[378]	Less than 80% were ≥1 month to <36 months
Elterman et al. (1999)[379]	Less than 80% were ≥1 month to <36 months
Endoh et al. (2012)[380]	Less than 80% were ≥1 month to <36 months
Englot et al. (2014)[381]	Less than 80% were ≥1 month to <36 months
Englot et al. (2017)[382]	Less than 80% were ≥1 month to <36 months
Erdemir et al. (2009)[383]	Less than 80% were ≥1 month to <36 months
Erdemir et al. (2021)[384]	Seizure type outside the scope (E.g., West syndrome, infantile spasms)
Eriksson et al. (1999)[385]	Less than 80% were ≥1 month to <36 months
Erturk et al. (2015)[386]	Less than 80% were ≥1 month to <36 months
Eschbach et al. (2017)[387]	No intervention (just describes patients)
Espeche et al. (2010)[388]	No outcomes of interest
Espinosa et al. (2008)[389]	Less than 80% were ≥1 month to <36 months
Eun et al. (2011)[390]	Less than 80% were ≥1 month to <36 months
Eun et al. (2012)[391]	Less than 80% were ≥1 month to <36 months
Evangeliou et al. (2009)[392]	N of 4-29 nonsurgery
Fallah et al. (2006)[393]	Less than 80% were ≥1 month to <36 months
Fallah et al. (2008)[394]	Less than 80% were ≥1 month to <36 months
Fallah et al. (2009)[395]	Less than 80% were ≥1 month to <36 months
Fallah et al. (2010)[396]	Less than 80% were ≥1 month to <36 months
Fallah et al. (2015)[397]	Less than 80% were ≥1 month to <36 months
Fallah et al. (2015)[398]	Less than 80% were ≥1 month to <36 months
Fallah et al. (2016)[399]	Age at treatment not reported
Falsaperla et al. (2017)[400]	Neonates
Falsaperla et al. (2019)[401]	Neonates
Fang et al. (2020)[402]	Less than 80% were ≥1 month to <36 months
Farasat et al. (2006)[403]	Less than 80% were ≥1 month to <36 months
Farhat et al. (2002)[404]	Less than 80% were ≥1 month to <36 months
Farias-Moeller et al. (2017)[405]	Case report (N=3 or fewer)
Farrace et al. (2013)[406]	Mean age 2 years and 4 months (range 8 months to 8 years); no further info provided
Fatema et al. (2015)[407]	Less than 80% were ≥1 month to <36 months
Fejerman et al. (2005)[408]	Narrative review
Feng et al. (2018)[409]	Less than 80% were ≥1 month to <36 months
Fernandes et al. (2021)[410]	Less than 80% were ≥1 month to <36 months
Fernandez et al. (2015)[411]	N of 4-29 nonsurgery

Study	Reason for Exclusion
Fernández-Concepción et al. (2021)[412]	Less than 80% were ≥1 month to <36 months
Ferrand-Sorbets et al. (2020)[413]	Less than 80% were ≥1 month to <36 months
Ferrara et al. (2013)[414]	Less than 80% were ≥1 month to <36 months
Ferrari et al. (2012)[415]	Not in English
Ferreira et al. (2019)[416]	N of 4-29 nonsurgery
Fisher et al. (2000)[417]	Less than 80% were ≥1 month to <36 months
Fitzgerald et al. (2019)[418]	Less than 80% were ≥1 month to <36 months
Fohlen et al. (2003)[419]	Less than 80% were ≥1 month to <36 months
Fonseca et al. (2007)[420]	Less than 80% were ≥1 month to <36 months
Fonseca Wald et al. (2019)[421]	Less than 80% were ≥1 month to <36 months
Francione et al. (2003)[422]	N of 4-29 nonsurgery
Frank-Briggs et al. (2011)[423]	Survey of parent knowledge of epilepsy
Franz et al. (2001)[424]	Less than 80% were ≥1 month to <36 months
Franzoni et al. (2006)[425]	Less than 80% were ≥1 month to <36 months
Franzoni et al. (2007)[426]	Less than 80% were ≥1 month to <36 months
Franzoni et al. (2009)[427]	Less than 80% were ≥1 month to <36 months
Freeman et al. (1998)[428]	N of 4-29 nonsurgery
Freeman et al. (1999)[429]	N of 4-29 nonsurgery
Freeman et al. (1999)[430]	Less than 80% were ≥1 month to <36 months
Freeman et al. (2009)[431]	Less than 80% were ≥1 month to <36 months
Freeman et al. (2018)[432]	Less than 80% were ≥1 month to <36 months
Freitas et al. (2007)[433]	Less than 80% were ≥1 month to <36 months
Friedman et al. (2013)[434]	Less than 80% were ≥1 month to <36 months
Frost et al. (2001)[435]	Less than 80% were ≥1 month to <36 months
Fujimoto et al. (2020)[436]	Less than 80% were ≥1 month to <36 months
Fujiwara et al. (2012)[437]	Less than 80% were ≥1 month to <36 months
Fujiwara et al. (2019)[438]	Less than 80% were ≥1 month to <36 months
Fukasawa et al. (2014)[439]	Data not specific to a treatment
Fukui et al. (2014)[440]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Fung et al. (2003)[441]	Less than 80% were ≥1 month to <36 months
Fung et al. (2019)[442]	Treatment to halt acute seizures (not prevention)
Gadgil et al. (2020)[443]	Not a treatment of interest
Gallentine et al. (2009)[444]	Treatment to halt acute seizures (not prevention)
Garoufi et al. (2014)[445]	Less than 80% were ≥1 month to <36 months
Gashlan et al. (1999)[446]	Less than 80% were ≥1 month to <36 months
Gasparini et al. (2016)[447]	Less than 80% were ≥1 month to <36 months
Gates et al. (2002)[448]	Less than 80% were ≥1 month to <36 months
Gavatha et al. (2011)[449]	Less than 80% were ≥1 month to <36 months
Geda et al. (2002)[450]	Less than 80% were ≥1 month to <36 months
Gedela et al. (2019)[451]	Less than 80% were ≥1 month to <36 months
Geerts et al. (2010)[452]	Less than 80% were ≥1 month to <36 months
Geffrey et al. (2015)[453]	Less than 80% were ≥1 month to <36 months
Gelinas et al. (2011)[454]	Less than 80% were ≥1 month to <36 months
Gerber et al. (2000)[455]	Less than 80% were ≥1 month to <36 months
Gerges et al. (2019)[456]	Less than 80% were ≥1 month to <36 months
Gericke et al. (1999)[457]	Less than 80% were ≥1 month to <36 months
Gerstner et al. (2006)[458]	Less than 80% were ≥1 month to <36 months
Gerstner et al. (2006)[459]	Less than 80% were ≥1 month to <36 months
Ghaffar et al. (2020)[460]	Neonates
Gharibnaseri et al. (2012)[461]	Less than 80% were ≥1 month to <36 months
Ghatan et al. (2014)[462]	N<10 surgery
Ghosh et al. (2019)[463]	Neonates
Gilbert et al. (2000)[464]	Age at treatment not reported
Gil-Nagel et al. (2021)[465]	Duplicate of [466]
Gil-Nagel et al. (2021)[466]	Less than 80% were ≥1 month to <36 months
Giordano et al. (2013)[467]	Case report (N=3 or fewer)
Girgis et al. (2010)[468]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Giroux et al. (2009)[469]	Less than 80% were ≥1 month to <36 months
Giulioni et al. (2013)[470]	Less than 80% were ≥1 month to <36 months
Giva et al. (2020)[471]	Systematic literature review
Glass et al. (2019)[472]	Neonates
Glauser et al. (2007)[473]	Followup NR or followup < 12 weeks
Glauser et al. (2010)[474]	Less than 80% were ≥1 month to <36 months
Glauser et al. (2013)[475]	Less than 80% were ≥1 month to <36 months
Glaze et al. (2010)[476]	No intervention (just describes patients)
Gleissner et al. (2006)[477]	Less than 80% were ≥1 month to <36 months
Gleissner et al. (2008)[478]	Less than 80% were ≥1 month to <36 months
Goellner et al. (2013)[479]	Less than 80% were ≥1 month to <36 months
Goldstein et al. (2018)[480]	Less than 80% were ≥1 month to <36 months
Gong et al. (2020)[481]	Less than 80% were ≥1 month to <36 months
González-Martínez et al. (2005)[482]	Patients overlapped with another included publication[483]
Goradia et al. (2011)[484]	Case report (N=3 or fewer)
Govil-Dalela et al. (2017)[485]	Less than 80% were ≥1 month to <36 months
Gowda et al. (2010)[486]	Patients overlapped with another included publication[483]
Gowda et al. (2019)[487]	Neonates
Grayson et al. (2020)[488]	N<10 surgery
Grayson et al. (2021)[489]	Less than 80% were ≥1 month to <36 months
Greiner et al. (2014)[490]	Less than 80% were ≥1 month to <36 months
Greiner et al. (2016)[491]	Less than 80% were ≥1 month to <36 months
Griffiths et al. (2007)[492]	Less than 80% were ≥1 month to <36 months
Groleau et al. (2014)[493]	Less than 80% were ≥1 month to <36 months
Grønborg et al. (2014)[494]	Only enrolled those who died
Gröppel et al. (2015)[495]	N<10 surgery
Gröppel et al. (2018)[496]	No outcomes reported for hemispherotomy patients, the only procedure with n>10
Gröppel et al. (2019)[497]	Less than 80% were ≥1 month to <36 months
Grosso et al. (2005)[498]	Less than 80% were ≥1 month to <36 months
Grosso et al. (2007)[499]	Less than 80% were ≥1 month to <36 months
Grosso et al. (2008)[500]	N of 4-29 nonsurgery
Grosso et al. (2008)[501]	Case report (N=3 or fewer)
Grosso et al. (2011)[502]	Less than 80% were ≥1 month to <36 months
Grosso et al. (2014)[503]	Less than 80% were ≥1 month to <36 months
Grosso et al. (2014)[504]	Less than 80% were ≥1 month to <36 months
Grosso et al. (2014)[505]	Less than 80% were ≥1 month to <36 months
Gross-Tsur et al. (2000)[506]	Less than 80% were ≥1 month to <36 months
Guan et al. (2017)[507]	Less than 80% were ≥1 month to <36 months
Guerrini et al. (2005)[508]	Less than 80% were ≥1 month to <36 months
Guerrini et al. (2014)[509]	Less than 80% were ≥1 month to <36 months
Guillet et al. (2007)[510]	Neonates
Gulati et al. (2015)[511]	Less than 80% were ≥1 month to <36 months
Günbey et al. (2020)[512]	Less than 80% were ≥1 month to <36 months
Gupta et al. (2004)[513]	Less than 80% were ≥1 month to <36 months
Gupta et al. (2004)[514]	Less than 80% were ≥1 month to <36 months
Gupta et al. (2006)[515]	No outcomes of interest
Gupta et al. (2007)[516]	Less than 80% were ≥1 month to <36 months
Gupta et al. (2021)[517]	Less than 80% were ≥1 month to <36 months
Gurbani et al. (2016)[518]	Less than 80% were ≥1 month to <36 months
Gurbani et al. (2020)[519]	Less than 80% were ≥1 month to <36 months
Guzel et al. (2019)[520]	Less than 80% were ≥1 month to <36 months
Habib et al. (2006)[521]	Less than 80% were ≥1 month to <36 months
Hadzagic-Catibusic et al. (2017)[522]	Less than 80% were ≥1 month to <36 months
Haerian et al. (2012)[523]	Less than 80% were ≥1 month to <36 months
Haig et al. (2001)[524]	Less than 80% were ≥1 month to <36 months
Hallböök et al. (2005)[525]	Less than 80% were ≥1 month to <36 months
Hallböök et al. (2005)[526]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Hallböök et al. (2005)[527]	Less than 80% were ≥1 month to <36 months
Hallböök et al. (2007)[528]	Case report (N=3 or fewer)
Hallböök et al. (2007)[529]	Less than 80% were ≥1 month to <36 months
Hallböök et al. (2013)[530]	Less than 80% were ≥1 month to <36 months
Hallböök et al. (2015)[531]	Less than 80% were ≥1 month to <36 months
Halley et al. (2010)[532]	Less than 80% were ≥1 month to <36 months
Hallioglu et al. (2008)[533]	Less than 80% were ≥1 month to <36 months
Hamad et al. (2013)[534]	Less than 80% were ≥1 month to <36 months
Hamed et al. (2009)[535]	Less than 80% were ≥1 month to <36 months
Hamed et al. (2012)[536]	Less than 80% were ≥1 month to <36 months
Han et al. (2018)[537]	Less than 80% were ≥1 month to <36 months
Han et al. (2018)[538]	Neonates
Haney et al. (2019)[539]	Less than 80% were ≥1 month to <36 months
Hannan et al. (2009)[540]	Case report (N=3 or fewer)
Harris et al. (2020)[541]	Systematic review or meta-analysis
Hartley et al. (2002)[542]	Less than 80% were ≥1 month to <36 months
Hasan et al. (2010)[543]	Less than 80% were ≥1 month to <36 months
Hasegawa et al. (2021)[544]	Less than 80% were ≥1 month to <36 months
Hassan et al. (1999)[545]	Less than 80% were ≥1 month to <36 months
Hassan et al. (2003)[546]	Less than 80% were ≥1 month to <36 months
Hauptman et al. (2012)[547]	Less than 80% were ≥1 month to <36 months
Hauptman et al. (2012)[548]	Less than 80% were ≥1 month to <36 months
Hausman-Kedem et al. (2017)[549]	Narrative review
Hausman-Kedem et al. (2018)[550]	Less than 80% were ≥1 month to <36 months
Havali et al. (2015)[551]	Less than 80% were ≥1 month to <36 months
Haznedar et al. (2019)[552]	Less than 80% were ≥1 month to <36 months
He et al. (2013)[553]	Less than 80% were ≥1 month to <36 months
He et al. (2015)[554]	Protocol only
Healy et al. (2013)[555]	Less than 80% were ≥1 month to <36 months
Hee et al. (2007)[556]	Less than 80% were ≥1 month to <36 months
Helmers et al. (2012)[557]	Less than 80% were ≥1 month to <36 months
Hemb et al. (2010)[558]	Less than 80% were ≥1 month to <36 months
Henderson et al. (2006)[559]	Systematic review or meta-analysis
Henkin et al. (2005)[560]	Less than 80% were ≥1 month to <36 months
Heo et al. (2017)[561]	Less than 80% were ≥1 month to <36 months
Herrero et al. (2020)[562]	Less than 80% were ≥1 month to <36 months
Hess et al. (2016)[563]	Less than 80% were ≥1 month to <36 months
Heyman et al. (2012)[564]	Less than 80% were ≥1 month to <36 months
Heyman et al. (2014)[565]	Less than 80% were ≥1 month to <36 months
Heyman et al. (2017)[566]	Less than 80% were ≥1 month to <36 months
Hidalgo et al. (2018)[567]	No outcomes of interest
Hiremath et al. (2005)[568]	Less than 80% were ≥1 month to <36 months
Hirfanoglu et al. (2016)[569]	Less than 80% were ≥1 month to <36 months
Hirfanoglu et al. (2018)[570]	Less than 80% were ≥1 month to <36 months
Hmaimess et al. (2020)[571]	Less than 80% were ≥1 month to <36 months
Hnaini et al. (2020)[572]	Neonates
Hodaie et al. (2001)[573]	Less than 80% were ≥1 month to <36 months
Holden et al. (1999)[574]	Less than 80% were ≥1 month to <36 months
Holtmann et al. (2002)[575]	Less than 80% were ≥1 month to <36 months
Honda et al. (2013)[576]	Patients overlapped with another included publication[577]
Honda et al. (2021)[578]	Less than 80% were ≥1 month to <36 months
Hoppe et al. (2019)[579]	Less than 80% were ≥1 month to <36 months
Hoppen et al. (2001)[580]	Neonates
Horacio Caraballo et al. (2011)[581]	N of 4-29 nonsurgery
Hori et al. (1999)[582]	Less than 80% were ≥1 month to <36 months
Hosain et al. (2005)[583]	N of 4-29 nonsurgery
Hu et al. (2012)[584]	Less than 80% were ≥1 month to <36 months
Hudgins et al. (2005)[585]	N<10 surgery

Study	Reason for Exclusion
Huppke et al. (2007)[586]	Less than 80% were ≥1 month to <36 months
Hur et al. (2018)[587]	Less than 80% were ≥1 month to <36 months
Hussain et al. (2015)[588]	Less than 80% were ≥1 month to <36 months
Hussain et al. (2016)[589]	Less than 80% were ≥1 month to <36 months
Hussain et al. (2020)[590]	Seizure type outside the scope (E.g., West syndrome, infantile spasms)
Hwang et al. (2012)[591]	Less than 80% were ≥1 month to <36 months
Hyslop et al. (2015)[592]	Less than 80% were ≥1 month to <36 months
Iannelli et al. (2000)[593]	N<10 surgery
Iannone et al. (2021)[594]	Less than 80% were ≥1 month to <36 months
Ibrahim et al. (2012)[595]	Less than 80% were ≥1 month to <36 months
Ibrahim et al. (2015)[596]	Less than 80% were ≥1 month to <36 months
Ibrahim et al. (2017)[597]	No outcomes of interest
Iimura et al. (2017)[598]	Less than 80% were ≥1 month to <36 months
Iinuma et al. (2004)[599]	N of 4-29 nonsurgery
IJff et al. (2016)[600]	Less than 80% were ≥1 month to <36 months
Ikegaya et al. (2020)[601]	N<10 surgery
Ikemoto et al. (2019)[602]	Less than 80% were ≥1 month to <36 months
Ilic et al. (2016)[603]	No outcomes of interest
Incecik et al. (2007)[604]	Less than 80% were ≥1 month to <36 months
Incecik et al. (2012)[605]	Less than 80% were ≥1 month to <36 months
Incecik et al. (2012)[606]	Less than 80% were ≥1 month to <36 months
Inoue et al. (2009)[607]	Less than 80% were ≥1 month to <36 months
Inoue et al. (2014)[608]	Less than 80% were ≥1 month to <36 months
Inoue et al. (2015)[609]	Less than 80% were ≥1 month to <36 months
Ipingbemi et al. (2015)[610]	Age at treatment not reported
Irshaid et al. (2004)[611]	Out of scope
Isgüder et al. (2014)[612]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Ishikawa et al. (2019)[613]	Less than 80% were ≥1 month to <36 months
Ishikawa et al. (2020)[614]	Less than 80% were ≥1 month to <36 months
Ismayilova et al. (2018)[615]	N of 4-29 nonsurgery
Itamura et al. (2019)[616]	Less than 80% were ≥1 month to <36 months
Itoh et al. (2015)[617]	No intervention (just describes patients)
Iwasaki et al. (2013)[618]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Iwasaki et al. (2015)[619]	Less than 80% were ≥1 month to <36 months
Iwasaki et al. (2016)[620]	Less than 80% were ≥1 month to <36 months
Jacobs et al. (2018)[621]	N<10 surgery
Jagadish et al. (2019)[622]	Less than 80% were ≥1 month to <36 months
Jagtap et al. (2013)[623]	No intervention (just describes patients)
Jain et al. (2011)[624]	Less than 80% were ≥1 month to <36 months
Jain et al. (2020)[625]	Less than 80% were ≥1 month to <36 months
Jakobsen et al. (2020)[626]	Less than 80% were ≥1 month to <36 months
Jalloh et al. (2018)[627]	Less than 80% were ≥1 month to <36 months
Jambaqué et al. (2000)[628]	N of 4-29 nonsurgery
Jambaqué et al. (2007)[629]	Less than 80% were ≥1 month to <36 months
Jan et al. (2000)[630]	Less than 80% were ≥1 month to <36 months
Jansen et al. (2007)[631]	N<10 surgery
Jayakar et al. (2008)[632]	Less than 80% were ≥1 month to <36 months
Jayalakshmi et al. (2011)[633]	Less than 80% were ≥1 month to <36 months
Jayalakshmi et al. (2019)[634]	Less than 80% were ≥1 month to <36 months
Jayawant et al. (2003)[635]	Less than 80% were ≥1 month to <36 months
Jedrzejczak et al. (2008)[636]	Less than 80% were ≥1 month to <36 months
Jehi et al. (2012)[637]	Less than 80% were ≥1 month to <36 months
Jennesson et al. (2013)[638]	Less than 80% were ≥1 month to <36 months
Jennum et al. (2016)[639]	Less than 80% were ≥1 month to <36 months
Jenny et al. (2016)[640]	Less than 80% were ≥1 month to <36 months
Jha et al. (2014)[641]	Narrative review
Ji et al. (2019)[642]	Less than 80% were ≥1 month to <36 months
Jo et al. (2013)[643]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Jonas et al. (2005)[644]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Joseph et al. (2011)[645]	Less than 80% were ≥1 month to <36 months
Juhasz et al. (2001)[646]	N of 4-29 nonsurgery
Jun et al. (2019)[647]	Less than 80% were ≥1 month to <36 months
Jung et al. (2008)[648]	Less than 80% were ≥1 month to <36 months
Jung et al. (2011)[649]	Less than 80% were ≥1 month to <36 months
Jung et al. (2012)[650]	Less than 80% were ≥1 month to <36 months
Junna et al. (2013)[651]	Less than 80% were ≥1 month to <36 months
Kabir et al. (2009)[652]	Less than 80% were ≥1 month to <36 months
Kadish et al. (2020)[653]	Less than 80% were ≥1 month to <36 months
Kafadar et al. (2014)[654]	Less than 80% were ≥1 month to <36 months
Kagawa et al. (2005)[655]	Less than 80% were ≥1 month to <36 months
Kalanithi et al. (2014)[656]	Less than 80% were ≥1 month to <36 months
Kaleyias et al. (2006)[657]	N of 4-29 nonsurgery
Kalra et al. (2010)[658]	Less than 80% were ≥1 month to <36 months
Kan et al. (2008)[659]	Less than 80% were ≥1 month to <36 months
Kanai et al. (2019)[660]	N of 4-29 nonsurgery
Kanai et al. (2020)[661]	Less than 80% were ≥1 month to <36 months
Kanemura et al. (2012)[662]	Less than 80% were ≥1 month to <36 months
Kanemura et al. (2013)[663]	Less than 80% were ≥1 month to <36 months
Kanemura et al. (2014)[664]	Less than 80% were ≥1 month to <36 months
Kanemura et al. (2014)[665]	Less than 80% were ≥1 month to <36 months
Kanemura et al. (2014)[665]	Duplicate
Kanemura et al. (2018)[666]	Less than 80% were ≥1 month to <36 months
Kang et al. (2006)[667]	Narrative review
Kang et al. (2006)[668]	Case report (N=3 or fewer)
Kang et al. (2007)[669]	Less than 80% were ≥1 month to <36 months
Kang et al. (2007)[670]	N of 4-29 nonsurgery
Kang et al. (2007)[671]	Less than 80% were ≥1 month to <36 months
Kankirawatana et al. (2001)[672]	Less than 80% were ≥1 month to <36 months
Kanmaz et al. (2020)[673]	Neonates
Karabiber et al. (2003)[674]	Age at treatment not reported
Karabiber et al. (2004)[675]	Less than 80% were ≥1 month to <36 months
Karaoglu et al. (2009)[676]	Less than 80% were ≥1 month to <36 months
Karaoglu et al. (2020)[677]	Neonates
Karaoglu et al. (2021)[678]	Results not specific to a treatment
Karatoprak et al. (2021)[679]	Less than 80% were ≥1 month to <36 months
Karimzadeh et al. (2013)[680]	Less than 80% were ≥1 month to <36 months
Karimzadeh et al. (2014)[681]	Less than 80% were ≥1 month to <36 months
Karimzadeh et al. (2019)[682]	1 arm had outcome data on only 2 patients, and the other arm had N<30
Kariuki et al. (2012)[683]	No intervention (just describes patients)
Katyal et al. (2000)[684]	Less than 80% were ≥1 month to <36 months
Kaushik et al. (2019)[685]	Less than 80% were ≥1 month to <36 months
Kawada et al. (2011)[686]	Neonates
Kayyali et al. (2020)[687]	Less than 80% were ≥1 month to <36 months
Kessi et al. (2021)[688]	Less than 80% were ≥1 month to <36 months
Kessler et al. (2011)[689]	Less than 80% were ≥1 month to <36 months
Kessler et al. (2015)[690]	Less than 80% were ≥1 month to <36 months
Kestle et al. (2000)[691]	Less than 80% were ≥1 month to <36 months
Khajavi et al. (1999)[692]	Case report (N=3 or fewer)
Khan et al. (2004)[693]	Less than 80% were ≥1 month to <36 months
Khan et al. (2006)[694]	Less than 80% were ≥1 month to <36 months
Khan et al. (2011)[695]	Neonates
Khan et al. (2013)[696]	Neonates
Khateeb et al. (2019)[697]	Less than 80% were ≥1 month to <36 months
Khoo et al. (2016)[698]	Less than 80% were ≥1 month to <36 months
Kikuchi et al. (2011)[699]	N of 4-29 nonsurgery
Kikuchi et al. (2017)[700]	Treatment to halt acute seizures (not prevention)

Study	Reason for Exclusion
Kilaru et al. (2007)[701]	Less than 80% were ≥1 month to <36 months
Kim et al. (2000)[702]	Less than 80% were ≥1 month to <36 months
Kim et al. (2001)[703]	N<10 surgery
Kim et al. (2005)[704]	Less than 80% were ≥1 month to <36 months
Kim et al. (2008)[705]	Less than 80% were ≥1 month to <36 months
Kim et al. (2009)[706]	Less than 80% were ≥1 month to <36 months
Kim et al. (2012)[707]	Less than 80% were ≥1 month to <36 months
Kim et al. (2012)[708]	Less than 80% were ≥1 month to <36 months
Kim et al. (2013)[709]	Less than 80% were ≥1 month to <36 months
Kim et al. (2014)[710]	Less than 80% were ≥1 month to <36 months
Kim et al. (2014)[711]	Less than 80% were ≥1 month to <36 months
Kim et al. (2018)[712]	Less than 80% were ≥1 month to <36 months
Kim et al. (2020)[713]	Less than 80% were ≥1 month to <36 months
Kim et al. (2021)[714]	No outcome data for any specific treatment
Kimura et al. (2014)[715]	Less than 80% were ≥1 month to <36 months
Kimura et al. (2019)[716]	Less than 80% were ≥1 month to <36 months
Kirkham et al. (2020)[717]	Less than 80% were ≥1 month to <36 months
Kishima et al. (2013)[718]	N<10 surgery
Klinkenberg et al. (2014)[719]	Less than 80% were ≥1 month to <36 months
Kloss et al. (2002)[720]	Less than 80% were ≥1 month to <36 months
Kluger et al. (2009)[721]	Less than 80% were ≥1 month to <36 months
Kluger et al. (2010)[722]	Less than 80% were ≥1 month to <36 months
Knorr et al. (2020)[723]	N of 4-29 nonsurgery
Knudsen et al. (2003)[724]	Case report (N=3 or fewer)
Ko et al. (2019)[725]	Less than 80% were ≥1 month to <36 months
Kodama et al. (2002)[726]	Less than 80% were ≥1 month to <36 months
Koh et al. (2000)[727]	Less than 80% were ≥1 month to <36 months
Koh et al. (2004)[728]	Less than 80% were ≥1 month to <36 months
Koh et al. (2005)[729]	Treatment to halt acute seizures (not prevention)
Kohrman et al. (2015)[730]	Less than 80% were ≥1 month to <36 months
König et al. (2003)[731]	Less than 80% were ≥1 month to <36 months
Korff et al. (2007)[732]	N of 4-29 nonsurgery
Koristkova et al. (2019)[733]	Less than 80% were ≥1 month to <36 months
Korneluk et al. (2003)[734]	Less than 80% were ≥1 month to <36 months
Korn-Merker et al. (2000)[735]	Less than 80% were ≥1 month to <36 months
KÖse et al. (2009)[736]	Less than 80% were ≥1 month to <36 months
Kossoff et al. (2004)[737]	Less than 80% were ≥1 month to <36 months
Kossoff et al. (2008)[738]	Less than 80% were ≥1 month to <36 months
Kossoff et al. (2010)[739]	Less than 80% were ≥1 month to <36 months
Kossoff et al. (2011)[740]	Less than 80% were ≥1 month to <36 months
Kothare et al. (2017)[741]	Narrative review
Kotulska et al. (2014)[742]	Data not specific to a treatment
Koubeissi et al. (2009)[743]	Less than 80% were ≥1 month to <36 months
Koubeissi et al. (2017)[744]	Narrative review
Koul et al. (2001)[745]	Less than 80% were ≥1 month to <36 months
Koutroumanidis et al. (2003)[746]	Less than 80% were ≥1 month to <36 months
Krajnc et al. (2011)[747]	Less than 80% were ≥1 month to <36 months
Kramer et al. (2000)[748]	N<10 surgery
Kramer et al. (2002)[749]	Age at treatment not reported
Kramer et al. (2006)[750]	Not a treatment of interest
Kramer et al. (2009)[751]	Treatment to halt acute seizures (not prevention)
Kravljanac et al. (2011)[752]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Kremenchugskaya et al. (2013)[753]	Not in English
Krief et al. (2008)[754]	N of 4-29 nonsurgery
Kröll-Seger et al. (2006)[755]	Less than 80% were ≥1 month to <36 months
Krsek et al. (2009)[756]	Less than 80% were ≥1 month to <36 months
Krsek et al. (2013)[757]	Less than 80% were ≥1 month to <36 months
Krueger et al. (2013)[758]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Kuehn et al. (2002)[759]	Less than 80% were ≥1 month to <36 months
Kumada et al. (2018)[760]	Less than 80% were ≥1 month to <36 months
Kurth et al. (2010)[761]	Less than 80% were ≥1 month to <36 months
Kurul et al. (2003)[762]	Less than 80% were ≥1 month to <36 months
Kurul et al. (2007)[763]	Less than 80% were ≥1 month to <36 months
Kurwale et al. (2020)[764]	Less than 80% were ≥1 month to <36 months
Kwan et al. (2000)[765]	Less than 80% were ≥1 month to <36 months
Kwan et al. (2006)[766]	Less than 80% were ≥1 month to <36 months
Kwan et al. (2010)[767]	Less than 80% were ≥1 month to <36 months
Kwon et al. (2016)[768]	Less than 80% were ≥1 month to <36 months
Kwon et al. (2020)[769]	Less than 80% were ≥1 month to <36 months
La Marca et al. (2013)[770]	N of 4-29 nonsurgery
Labar et al. (2000)[771]	Narrative review
Lachhwani et al. (2008)[772]	Less than 80% were ≥1 month to <36 months
Laffond et al. (2012)[773]	Less than 80% were ≥1 month to <36 months
Lagae et al. (2003)[774]	Case report (N=3 or fewer)
Lagae et al. (2012)[775]	Not in English
Lagae et al. (2015)[776]	Less than 80% were ≥1 month to <36 months
Lagae et al. (2018)[777]	Data not specific to a treatment
Lagae et al. (2019)[778]	Less than 80% were ≥1 month to <36 months
Lagae et al. (2019)[779]	Age at treatment not reported
Lagunju et al. (2011)[780]	Less than 80% were ≥1 month to <36 months
Lah et al. (2015)[781]	Less than 80% were ≥1 month to <36 months
Lakshminarayanan et al. (2021)[782]	Less than 80% were ≥1 month to <36 months
Lamb et al. (2020)[783]	Comment/guideline/position statement/editorial
Lamberink et al. (2015)[784]	Less than 80% were ≥1 month to <36 months
Lambrechts et al. (2015)[785]	Less than 80% were ≥1 month to <36 months
Lambrechts et al. (2017)[786]	Less than 80% were ≥1 month to <36 months
Larson et al. (2012)[787]	Less than 80% were ≥1 month to <36 months
Larsson et al. (2010)[788]	Less than 80% were ≥1 month to <36 months
Larsson et al. (2012)[789]	Less than 80% were ≥1 month to <36 months
Larysz et al. (2007)[790]	Less than 80% were ≥1 month to <36 months
Laux et al. (2019)[791]	Less than 80% were ≥1 month to <36 months
Law et al. (2015)[792]	Less than 80% were ≥1 month to <36 months
Law et al. (2017)[793]	Less than 80% were ≥1 month to <36 months
Lawden et al. (1999)[794]	Less than 80% were ≥1 month to <36 months
Lazaridis et al. (2019)[795]	Narrative review
Lazow et al. (2012)[796]	Less than 80% were ≥1 month to <36 months
Leal et al. (2020)[797]	Less than 80% were ≥1 month to <36 months
Lebowitz et al. (2016)[798]	Less than 80% were ≥1 month to <36 months
Lee et al. (2005)[799]	Less than 80% were ≥1 month to <36 months
Lee et al. (2008)[800]	Less than 80% were ≥1 month to <36 months
Lee et al. (2010)[801]	N of 4-29 nonsurgery
Lee et al. (2010)[802]	Less than 80% were ≥1 month to <36 months
Lee et al. (2010)[803]	Less than 80% were ≥1 month to <36 months
Lee et al. (2010)[804]	Less than 80% were ≥1 month to <36 months
Lee et al. (2011)[805]	Less than 80% were ≥1 month to <36 months
Lee et al. (2012)[806]	Less than 80% were ≥1 month to <36 months
Lee et al. (2013)[807]	Less than 80% were ≥1 month to <36 months
Lee et al. (2014)[808]	Less than 80% were ≥1 month to <36 months
Lee et al. (2016)[809]	Less than 80% were ≥1 month to <36 months
Lee et al. (2018)[810]	Less than 80% were ≥1 month to <36 months
Leiphart et al. (2001)[811]	Less than 80% were ≥1 month to <36 months
Lemmon et al. (2012)[812]	Less than 80% were ≥1 month to <36 months
Lendt et al. (2000)[813]	Less than 80% were ≥1 month to <36 months
Lendt et al. (2002)[814]	Less than 80% were ≥1 month to <36 months
Leonard et al. (2010)[815]	Less than 80% were ≥1 month to <36 months
Levy et al. (2010)[816]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Lew et al. (2014)[817]	Less than 80% were ≥1 month to <36 months
Lewena et al. (2006)[818]	Treatment to halt acute seizures (not prevention)
Li et al. (2004)[819]	Less than 80% were ≥1 month to <36 months
Li et al. (2009)[820]	Less than 80% were ≥1 month to <36 months
Li et al. (2010)[821]	N of 4-29 nonsurgery
Li et al. (2011)[822]	Less than 80% were ≥1 month to <36 months
Li et al. (2013)[823]	Less than 80% were ≥1 month to <36 months
Li et al. (2017)[824]	Less than 80% were ≥1 month to <36 months
Li et al. (2020)[825]	Less than 80% were ≥1 month to <36 months
Li et al. (2020)[826]	Less than 80% were ≥1 month to <36 months
Li et al. (2020)[827]	Less than 80% were ≥1 month to <36 months
Liang et al. (2018)[828]	No outcomes of interest
Liao et al. (2020)[829]	Less than 80% were ≥1 month to <36 months
Liasis et al. (2003)[830]	Case report (N=3 or fewer)
Liava et al. (2014)[831]	Less than 80% were ≥1 month to <36 months
Liava et al. (2016)[832]	Less than 80% were ≥1 month to <36 months
Licheni et al. (2018)[833]	Less than 80% were ≥1 month to <36 months
Liégeois et al. (2008)[834]	Less than 80% were ≥1 month to <36 months
Liguori et al. (2020)[835]	Less than 80% were ≥1 month to <36 months
Lim et al. (2017)[836]	Less than 80% were ≥1 month to <36 months
Lim et al. (2018)[837]	Less than 80% were ≥1 month to <36 months
Lim et al. (2021)[838]	Less than 80% were ≥1 month to <36 months
Lima-Rogel et al. (2018)[839]	Neonates
Limbrick et al. (2009)[840]	Less than 80% were ≥1 month to <36 months
Limbrick et al. (2009)[841]	Case report (N=3 or fewer)
Lin et al. (2002)[842]	Not in English
Lin et al. (2007)[843]	Less than 80% were ≥1 month to <36 months
Lin et al. (2012)[844]	Less than 80% were ≥1 month to <36 months
Lin et al. (2015)[845]	Less than 80% were ≥1 month to <36 months
Lin et al. (2018)[846]	Less than 80% were ≥1 month to <36 months
Lippé et al. (2010)[847]	N<10 surgery
Liu et al. (2002)[848]	Not in English
Liu et al. (2003)[849]	Not in English
Liu et al. (2003)[850]	Less than 80% were ≥1 month to <36 months
Liu et al. (2007)[851]	Less than 80% were ≥1 month to <36 months
Liu et al. (2012)[852]	Less than 80% were ≥1 month to <36 months
Liu et al. (2015)[853]	Less than 80% were ≥1 month to <36 months
Liu et al. (2016)[854]	Less than 80% were ≥1 month to <36 months
Liu et al. (2018)[855]	Less than 80% were ≥1 month to <36 months
Liu et al. (2019)[856]	N of 4-29 nonsurgery
Liu et al. (2019)[857]	Less than 80% were ≥1 month to <36 months
Liu et al. (2020)[858]	Less than 80% were ≥1 month to <36 months
Liu et al. (2020)[859]	Less than 80% were ≥1 month to <36 months
Liu et al. (2020)[860]	Neonates
Liu et al. (2021)[861]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Lloreda-García et al. (2017)[862]	Neonates
Lockney et al. (2017)[863]	They didnt have seizures at enrollment
Loddenkemper et al. (2012)[864]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Logroscino et al. (2002)[865]	Treatment to halt acute seizures (not prevention)
López et al. (2010)[866]	Less than 80% were ≥1 month to <36 months
Loring et al. (2001)[867]	Narrative review
Loring et al. (2020)[868]	Less than 80% were ≥1 month to <36 months
Lortie et al. (2002)[869]	N<10 surgery
Lou Smith et al. (2006)[870]	Less than 80% were ≥1 month to <36 months
Love et al. (2016)[871]	No intervention (just describes patients)
Low et al. (2016)[872]	Neonates
Lu et al. (2007)[873]	Less than 80% were ≥1 month to <36 months
Luat et al. (2018)[874]	No intervention (just describes patients)

Study	Reason for Exclusion
Lukka et al. (2021)[875]	Less than 80% were ≥1 month to <36 months
Luoni et al. (2015)[876]	Less than 80% were ≥1 month to <36 months
Luz et al. (2019)[877]	Less than 80% were ≥1 month to <36 months
Lyczkowski et al. (2005)[878]	Less than 80% were ≥1 month to <36 months
Ma et al. (2009)[879]	Less than 80% were ≥1 month to <36 months
Mackay et al. (2005)[880]	Less than 80% were ≥1 month to <36 months
Madan Cohen et al. (2021)[881]	Less than 80% were ≥1 month to <36 months
Madhavan et al. (2007)[882]	Less than 80% were ≥1 month to <36 months
Mahmoudian et al. (2005)[883]	Less than 80% were ≥1 month to <36 months
Maitre et al. (2013)[884]	Neonates
Majkowska-Zwolinska et al. (2012)[885]	Less than 80% were ≥1 month to <36 months
Majoie et al. (2005)[886]	Less than 80% were ≥1 month to <36 months
Makis et al. (2005)[887]	Less than 80% were ≥1 month to <36 months
Maksoud et al. (2016)[888]	Less than 80% were ≥1 month to <36 months
Malik et al. (2009)[889]	Unable to obtain
Malik et al. (2013)[890]	Case report (N=3 or fewer)
Malmgren et al. (2008)[891]	Less than 80% were ≥1 month to <36 months
Maloletnev et al. (2016)[892]	Less than 80% were ≥1 month to <36 months
Mandel et al. (2002)[893]	Less than 80% were ≥1 month to <36 months
Mandelbaum et al. (2005)[894]	Less than 80% were ≥1 month to <36 months
Mandelbaum et al. (2005)[895]	Less than 80% were ≥1 month to <36 months
Mandell et al. (2015)[896]	Less than 80% were ≥1 month to <36 months
Mani et al. (2006)[897]	Less than 80% were ≥1 month to <36 months
Mann et al. (2014)[898]	N of 4-29 nonsurgery
Mann et al. (2020)[899]	Less than 80% were ≥1 month to <36 months
Marashly et al. (2020)[900]	Case report (N=3 or fewer)
Marchiò et al. (2019)[901]	Less than 80% were ≥1 month to <36 months
Marino et al. (2018)[902]	Less than 80% were ≥1 month to <36 months
Marras et al. (2010)[903]	Less than 80% were ≥1 month to <36 months
Marsh et al. (2006)[904]	Less than 80% were ≥1 month to <36 months
Marson et al. (2007)[905]	Less than 80% were ≥1 month to <36 months
Martin et al. (2016)[906]	Less than 80% were ≥1 month to <36 months
Martinez et al. (2007)[907]	Less than 80% were ≥1 month to <36 months
Martínez-Ferrández et al. (2019)[908]	Less than 80% were ≥1 month to <36 months
Masino et al. (2021)[909]	Less than 80% were ≥1 month to <36 months
Masuccio et al. (2010)[910]	Less than 80% were ≥1 month to <36 months
Masur et al. (2013)[911]	Less than 80% were ≥1 month to <36 months
Mathern et al. (1999)[912]	Less than 80% were ≥1 month to <36 months
Mathew et al. (2012)[913]	Less than 80% were ≥1 month to <36 months
Mathew et al. (2020)[914]	Neonates
Mathiak et al. (2010)[915]	Less than 80% were ≥1 month to <36 months
Mathieson et al. (2016)[916]	Neonates
Maton et al. (2007)[917]	Case report (N=3 or fewer)
Matsufuji et al. (2005)[918]	N of 4-29 non-surgery
May et al. (2011)[919]	Less than 80% were ≥1 month to <36 months
May et al. (2012)[920]	Less than 80% were ≥1 month to <36 months
Maydell et al. (2001)[921]	N of 4-29 nonsurgery
Mazaheri et al. (2011)[922]	Less than 80% were ≥1 month to <36 months
Mazur et al. (2019)[923]	Less than 80% were ≥1 month to <36 months
McBride et al. (2000)[924]	Neonates
McCoy et al. (2011)[925]	Less than 80% were ≥1 month to <36 months
McCoy et al. (2018)[926]	Less than 80% were ≥1 month to <36 months
McDonald et al. (2005)[927]	Less than 80% were ≥1 month to <36 months
McDonald et al. (2017)[928]	No intervention (just describes patients)
McGinnis et al. (2016)[929]	Less than 80% were ≥1 month to <36 months
McNamara et al. (2013)[930]	Age at treatment not reported
McNamara et al. (2020)[931]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
McWilliams et al. (2016)[932]	No intervention (just describes patients)
Medeiros et al. (2016)[933]	Appears to be only an abstract but describes full paper. Also does not seem to report outcomes of interest
Meekes et al. (2013)[934]	Less than 80% were ≥1 month to <36 months
Meekes et al. (2014)[935]	Less than 80% were ≥1 month to <36 months
Meekes et al. (2015)[936]	Less than 80% were ≥1 month to <36 months
Mehta et al. (2016)[937]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Menascu et al. (2013)[938]	Less than 80% were ≥1 month to <36 months
Meng et al. (2015)[939]	Less than 80% were ≥1 month to <36 months
Mengesha et al. (2009)[940]	Less than 80% were ≥1 month to <36 months
Meral et al. (2011)[941]	Less than 80% were ≥1 month to <36 months
Metz-Lutz et al. (1999)[942]	Less than 80% were ≥1 month to <36 months
Miao et al. (2019)[943]	Less than 80% were ≥1 month to <36 months
Michaelides et al. (2008)[944]	Less than 80% were ≥1 month to <36 months
Michoulas et al. (2006)[945]	Less than 80% were ≥1 month to <36 months
Mikaeloff et al. (2003)[946]	Less than 80% were ≥1 month to <36 months
Mikati et al. (2002)[947]	N of 4-29 nonsurgery
Mikati et al. (2008)[948]	Less than 80% were ≥1 month to <36 months
Mikati et al. (2010)[949]	Less than 80% were ≥1 month to <36 months
Milano et al. (2021)[950]	Less than 80% were ≥1 month to <36 months
Milh et al. (2009)[951]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Miller et al. (2014)[952]	Comment/guideline/position statement/editorial
Mills et al. (2011)[953]	Less than 80% were ≥1 month to <36 months
Mills et al. (2012)[954]	Less than 80% were ≥1 month to <36 months
Mir et al. (2020)[955]	Less than 80% were ≥1 month to <36 months
Miranda et al. (2011)[956]	Less than 80% were ≥1 month to <36 months
Miró et al. (2014)[957]	Less than 80% were ≥1 month to <36 months
Miserocchi et al. (2013)[958]	Less than 80% were ≥1 month to <36 months
Mishra et al. (2011)[959]	Case report (N=3 or fewer)
Mishra et al. (2011)[960]	Less than 80% were ≥1 month to <36 months
Miskin et al. (2015)[961]	Less than 80% were ≥1 month to <36 months
Mittal et al. (2005)[962]	Less than 80% were ≥1 month to <36 months
Miura et al. (2004)[963]	Less than 80% were ≥1 month to <36 months
Miyamoto et al. (2000)[964]	Less than 80% were ≥1 month to <36 months
Moavero et al. (2020)[965]	No outcomes of interest
Modi et al. (2009)[966]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Modi et al. (2011)[967]	Less than 80% were ≥1 month to <36 months
Modi et al. (2014)[968]	Less than 80% were ≥1 month to <36 months
Mohammadreza et al. (2010)[969]	Less than 80% were ≥1 month to <36 months
Mohammed et al. (2006)[970]	Less than 80% were ≥1 month to <36 months
Mohan et al. (2019)[971]	Age at treatment not reported
Mollamohammadi et al. (2018)[972]	Neonates
Momen et al. (2018)[973]	Less than 80% were ≥1 month to <36 months
Moreland et al. (1999)[974]	Less than 80% were ≥1 month to <36 months
Moritake et al. (2008)[975]	Less than 80% were ≥1 month to <36 months
Morrison et al. (2009)[976]	Less than 80% were ≥1 month to <36 months
Morrison-Levy et al. (2018)[977]	Less than 80% were ≥1 month to <36 months
Morse et al. (2011)[978]	Narrative review
Moseley et al. (2012)[979]	Less than 80% were ≥1 month to <36 months
Moshel et al. (2010)[980]	N<10 surgery
Mueller et al. (2011)[981]	Less than 80% were ≥1 month to <36 months
Mühlebner et al. (2014)[982]	Less than 80% were ≥1 month to <36 months
Mühlebner et al. (2016)[983]	Less than 80% were ≥1 month to <36 months
Mujgan Sonmez et al. (2006)[984]	No outcomes of interest
Munari et al. (2000)[985]	Less than 80% were ≥1 month to <36 months
Muramatsu et al. (2017)[986]	Less than 80% were ≥1 month to <36 months
Murphy et al. (2003)[987]	Less than 80% were ≥1 month to <36 months
Musa-Veloso et al. (2006)[988]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Muthiah et al. (2020)[989]	Less than 80% were ≥1 month to <36 months
Muzykewicz et al. (2009)[990]	Less than 80% were ≥1 month to <36 months
Na et al. (2020)[991]	N of 4-29 nonsurgery
Nabangchang et al. (2005)[992]	Case report (N=3 or fewer)
Nabbout et al. (2020)[993]	Less than 80% were ≥1 month to <36 months
Nabbout et al. (2020)[994]	Less than 80% were ≥1 month to <36 months
Nadler et al. (2008)[995]	Less than 80% were ≥1 month to <36 months
Nagarajan et al. (2002)[996]	Less than 80% were ≥1 month to <36 months
Nagarajan et al. (2015)[997]	Less than 80% were ≥1 month to <36 months
Nakajima et al. (2011)[998]	Less than 80% were ≥1 month to <36 months
Nangia et al. (2012)[999]	Narrative review
Natarajan et al. (2018)[1000]	Neonates
Nathan et al. (2009)[1001]	Less than 80% were ≥1 month to <36 months
Nation et al. (2014)[1002]	No outcomes of interest
Naves et al. (2015)[1003]	Less than 80% were ≥1 month to <36 months
Nazziwa et al. (2014)[1004]	Less than 80% were ≥1 month to <36 months
Neal et al. (2008)[1005]	Less than 80% were ≥1 month to <36 months
Neal et al. (2009)[1006]	Less than 80% were ≥1 month to <36 months
Neininger et al. (2015)[1007]	Neonates
Nelles et al. (2015)[1008]	No outcomes of interest
Neubauer et al. (2018)[1009]	Less than 80% were ≥1 month to <36 months
Ng et al. (2002)[1010]	Not a treatment of interest
Ng et al. (2010)[1011]	N of 4-29 nonsurgery
Ng et al. (2011)[1012]	Less than 80% were ≥1 month to <36 months
Ng et al. (2012)[1013]	Less than 80% were ≥1 month to <36 months
Nguyen et al. (2020)[1014]	Age at treatment not reported
Nickels et al. (2017)[1015]	Narrative review
Nickels et al. (2020)[1016]	Narrative review
Nickels et al. (2020)[1017]	Comment/guideline/position statement/editorial
Nicolson et al. (2004)[1018]	Less than 80% were ≥1 month to <36 months
Nieto-Barrera et al. (2000)[1019]	Less than 80% were ≥1 month to <36 months
Nilsson et al. (2016)[1020]	Less than 80% were ≥1 month to <36 months
Nimaga et al. (2002)[1021]	Less than 80% were ≥1 month to <36 months
Nishikawa et al. (2020)[1022]	N of 4-29 non-surgery
Nishio et al. (2001)[1023]	Case report (N=3 or fewer)
No author et al. (2005)[1024]	Comment/guideline/position statement/editorial
No author et al. (2021)[1025]	Comment/guideline/position statement/editorial
Nolan et al. (2004)[1026]	Less than 80% were ≥1 month to <36 months
Nolan et al. (2019)[1027]	Less than 80% were ≥1 month to <36 months
Noli et al. (2013)[1028]	N<10 surgery
Nonoda et al. (2014)[1029]	Less than 80% were ≥1 month to <36 months
Nordli et al. (2001)[1030]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Northam et al. (2005)[1031]	N of 4-29 nonsurgery
Noureen et al. (2011)[1032]	Less than 80% were ≥1 month to <36 months
Novak et al. (1999)[1033]	Less than 80% were ≥1 month to <36 months
Novak et al. (2019)[1034]	Less than 80% were ≥1 month to <36 months
Obeid et al. (2010)[1035]	Less than 80% were ≥1 month to <36 months
Oesch et al. (2019)[1036]	Less than 80% were ≥1 month to <36 months
Ogiwara et al. (2010)[1037]	N<10 surgery
Oguni et al. (2002)[1038]	Less than 80% were ≥1 month to <36 months
Ohtahara et al. (2004)[1039]	Less than 80% were ≥1 month to <36 months
Oitment et al. (2013)[1040]	Less than 80% were ≥1 month to <36 months
Okanari et al. (2015)[1041]	Less than 80% were ≥1 month to <36 months
Okanishi et al. (2018)[1042]	Less than 80% were ≥1 month to <36 months
Okumura et al. (2006)[1043]	N of 4-29 nonsurgery
Okumura et al. (2016)[1044]	N of 4-29 nonsurgery
Okumura et al. (2019)[1045]	Less than 80% were ≥1 month to <36 months
Oldham et al. (2015)[1046]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Ollivier et al. (2009)[1047]	Less than 80% were ≥1 month to <36 months
Olson et al. (2011)[1048]	Less than 80% were ≥1 month to <36 months
Olsson et al. (2013)[1049]	Less than 80% were ≥1 month to <36 months
Oluigbo et al. (2015)[1050]	Less than 80% were ≥1 month to <36 months
Öner et al. (2004)[1051]	Less than 80% were ≥1 month to <36 months
Ono et al. (2011)[1052]	Less than 80% were ≥1 month to <36 months
Operto et al. (2021)[1053]	Less than 80% were ≥1 month to <36 months
Opp et al. (2005)[1054]	Less than 80% were ≥1 month to <36 months
Orosz et al. (2014)[1055]	Less than 80% were ≥1 month to <36 months
Ostrovsky et al. (2018)[1056]	Comment/guideline/position statement/editorial
Otoul et al. (2007)[1057]	Less than 80% were ≥1 month to <36 months
Otsuki et al. (2016)[1058]	Less than 80% were ≥1 month to <36 months
Overwater et al. (2015)[1059]	Less than 80% were ≥1 month to <36 months
Özalkaya et al. (2019)[1060]	Neonates
Ozanne et al. (2018)[1061]	Parent, but not on their preferences
Ozcelik et al. (2014)[1062]	Less than 80% were ≥1 month to <36 months
Ozdemir et al. (2016)[1063]	Less than 80% were ≥1 month to <36 months
Ozerol et al. (2003)[1064]	No outcomes of interest
Ozerol et al. (2003)[1065]	Less than 80% were ≥1 month to <36 months
Pablos-Sánchez et al. (2014)[1066]	Not in English
Pacione et al. (2011)[1067]	Less than 80% were ≥1 month to <36 months
Painter et al. (1999)[1068]	Neonates
Pan et al. (2020)[1069]	Less than 80% were ≥1 month to <36 months
Panigrahi et al. (2016)[1070]	Less than 80% were ≥1 month to <36 months
Panomvana et al. (2006)[1071]	Less than 80% were ≥1 month to <36 months
Panov et al. (2020)[1072]	Less than 80% were ≥1 month to <36 months
Paolicchi et al. (2000)[1073]	Less than 80% were ≥1 month to <36 months
Paolicchi et al. (2015)[1074]	Less than 80% were ≥1 month to <36 months
Papazoglou et al. (2010)[1075]	Less than 80% were ≥1 month to <36 months
Parain et al. (2001)[1076]	Less than 80% were ≥1 month to <36 months
Park et al. (2003)[1077]	Less than 80% were ≥1 month to <36 months
Park et al. (2006)[1078]	Less than 80% were ≥1 month to <36 months
Park et al. (2007)[1079]	Less than 80% were ≥1 month to <36 months
Park et al. (2012)[1080]	Less than 80% were ≥1 month to <36 months
Park et al. (2020)[1081]	Less than 80% were ≥1 month to <36 months
Parker et al. (1999)[1082]	Less than 80% were ≥1 month to <36 months
Pasca et al. (2018)[1083]	Less than 80% were ≥1 month to <36 months
Patel et al. (2010)[1084]	Less than 80% were ≥1 month to <36 months
Patel et al. (2018)[1085]	Less than 80% were ≥1 month to <36 months
Patel et al. (2021)[1086]	Less than 80% were ≥1 month to <36 months
Pathak et al. (2013)[1087]	Neonates
Pati et al. (2011)[1088]	N<10 surgery
Pati et al. (2013)[1089]	Less than 80% were ≥1 month to <36 months
Patwardhan et al. (2000)[1090]	Less than 80% were ≥1 month to <36 months
Paul et al. (2010)[1091]	Less than 80% were ≥1 month to <36 months
Pavlou et al. (2012)[1092]	Less than 80% were ≥1 month to <36 months
Peake et al. (2007)[1093]	Less than 80% were ≥1 month to <36 months
Pearl et al. (2009)[1094]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Peker et al. (2009)[1095]	Less than 80% were ≥1 month to <36 months
Pelliccia et al. (2017)[1096]	Less than 80% were ≥1 month to <36 months
Pellock et al. (2011)[1097]	Less than 80% were ≥1 month to <36 months
Peng et al. (2021)[1098]	Less than 80% were ≥1 month to <36 months
Pereira et al. (2012)[1099]	Less than 80% were ≥1 month to <36 months
Perez et al. (1999)[1100]	Data not specific to a treatment
Perry et al. (2007)[1101]	Less than 80% were ≥1 month to <36 months
Perry et al. (2008)[1102]	Less than 80% were ≥1 month to <36 months
Perry et al. (2010)[1103]	Less than 80% were ≥1 month to <36 months
Perry et al. (2013)[1104]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Perry et al. (2017)[1105]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Perry et al. (2019)[1106]	Comment/guideline/position statement/editorial
Pestana Knight et al. (2011)[1107]	Less than 80% were ≥1 month to <36 months
Phillips et al. (2020)[1108]	Less than 80% were ≥1 month to <36 months
Phung et al. (2013)[1109]	Less than 80% were ≥1 month to <36 months
Pickrell et al. (2017)[1110]	Narrative review
Pietrafusa et al. (2019)[1111]	Less than 80% were ≥1 month to <36 months
Piña-Garza et al. (2005)[1112]	Followup NR or Followup <12 weeks
Piña-Garza et al. (2017)[1113]	Less than 80% were ≥1 month to <36 months
Piñea-Garza et al. (2009)[1114]	The only outcome reported for our age gorup was efficacy, but followup <12 weeks. The age 24-48 month was too large and included too many age ≥36 months.
Ping et al. (2009)[1115]	Less than 80% were ≥1 month to <36 months
Pirzadeh et al. (2017)[1116]	Less than 80% were ≥1 month to <36 months
Pisano et al. (2015)[1117]	Neonates
Pittau et al. (2009)[1118]	Less than 80% were ≥1 month to <36 months
Plosker et al. (2012)[1119]	Narrative review
Pomata et al. (2000)[1120]	Less than 80% were ≥1 month to <36 months
Pong et al. (2012)[1121]	Less than 80% were ≥1 month to <36 months
Poorshiri et al. (2021)[1122]	Less than 80% were ≥1 month to <36 months
Porat Rein et al. (2020)[1123]	No intervention (just describes patients)
Porcari et al. (2018)[1124]	Less than 80% were ≥1 month to <36 months
Porta et al. (2009)[1125]	N of 4-29 nonsurgery
Porter et al. (2003)[1126]	Less than 80% were ≥1 month to <36 months
Prablek et al. (2021)[1127]	Less than 80% were ≥1 month to <36 months
Prasad et al. (2001)[1128]	Less than 80% were ≥1 month to <36 months
Prayson et al. (1999)[1129]	No outcomes of interest
Press et al. (2015)[1130]	Less than 80% were ≥1 month to <36 months
Pressler et al. (2005)[1131]	Less than 80% were ≥1 month to <36 months
Pressler et al. (2006)[1132]	Less than 80% were ≥1 month to <36 months
Pressler et al. (2015)[1133]	Neonates
Prins et al. (2014)[1134]	Treatment to halt acute seizures (not prevention)
Procaccini et al. (2006)[1135]	N<10 surgery
Prodam et al. (2010)[1136]	No outcomes of interest
Pruvost et al. (2006)[1137]	Less than 80% were ≥1 month to <36 months
Puertas-Martín et al. (2014)[1138]	Not in English
Puka et al. (2015)[1139]	Less than 80% were ≥1 month to <36 months
Puka et al. (2016)[1140]	Less than 80% were ≥1 month to <36 months
Puka et al. (2016)[1141]	Less than 80% were ≥1 month to <36 months
Puka et al. (2016)[1142]	Less than 80% were ≥1 month to <36 months
Pulsifer et al. (2004)[1143]	Less than 80% were ≥1 month to <36 months
Purusothaman et al. (2014)[1144]	Out of scope
Putignano et al. (2017)[1145]	Less than 80% were ≥1 month to <36 months
Qiang et al. (2017)[1146]	Less than 80% were ≥1 month to <36 months
Qin et al. (2018)[1147]	Less than 80% were ≥1 month to <36 months
Radhakrishnan et al. (2018)[1148]	Less than 80% were ≥1 month to <36 months
Radhakrishnan et al. (2018)[1149]	Less than 80% were ≥1 month to <36 months
Rahimi et al. (2007)[1150]	N<10, surgery
Rahman et al. (2005)[1151]	Less than 80% were ≥1 month to <36 months
Raj et al. (2017)[1152]	Less than 80% were ≥1 month to <36 months
Rajalakshmi et al. (2014)[1153]	No intervention (just describes patients)
Raju et al. (2011)[1154]	Less than 80% were ≥1 month to <36 months
Rakshasbhuvankar et al. (2013)[1155]	Neonates
Ramachandrannair et al. (2007)[1156]	Less than 80% were ≥1 month to <36 months
Ramantani et al. (2011)[1157]	Neonates
Ramantani et al. (2013)[1158]	N<10 surgery
Ramantani et al. (2013)[1159]	Patients overlapped with another included publication[1160]
Ramantani et al. (2013)[1161]	Patients overlapped with another included publication[1160]

Study	Reason for Exclusion
Ramantani et al. (2014)[1162]	Less than 80% were ≥1 month to <36 months
Ramantani et al. (2020)[1163]	Comment/guideline/position statement/editorial
Ramos-Lizana et al. (2009)[1164]	Less than 80% were ≥1 month to <36 months
Rao et al. (2018)[1165]	Neonates
Rauchenzauner et al. (2008)[1166]	Less than 80% were ≥1 month to <36 months
Raut et al. (2016)[1167]	Less than 80% were ≥1 month to <36 months
Rawat et al. (2015)[1168]	Seizure type outside the scope (E.g., West syndrome, infantile spasms)
Reaven et al. (2018)[1169]	Less than 80% were ≥1 month to <36 months
Régis et al. (2007)[1170]	Narrative review
Rehman et al. (2017)[1171]	Less than 80% were ≥1 month to <36 months
Reilly et al. (2017)[1172]	Less than 80% were ≥1 month to <36 months
Reilly et al. (2020)[1173]	Less than 80% were ≥1 month to <36 months
Reinholdson et al. (2020)[1174]	Less than 80% were ≥1 month to <36 months
Reiter et al. (2004)[1175]	Less than 80% were ≥1 month to <36 months
Reith et al. (2003)[1176]	N of 4-29 nonsurgery
Reithmeier et al. (2018)[1177]	Protocol
Remahl et al. (2008)[1178]	Case report (N=3 or fewer)
Renfroe et al. (2019)[1179]	Less than 80% were ≥1 month to <36 months
Rey et al. (2004)[1180]	Less than 80% were ≥1 month to <36 months
Reyes-Pérez et al. (2006)[1181]	Less than 80% were ≥1 month to <36 months
Rezaei et al. (2017)[1182]	Less than 80% were ≥1 month to <36 months
Riantarini et al. (2019)[1183]	Data not specific to a treatment
Ricci et al. (2021)[1184]	Case report (N=3 or fewer)
Richards et al. (2010)[1185]	Narrative review
Riechmann et al. (2015)[1186]	Less than 80% were ≥1 month to <36 months
Robert-Boire et al. (2019)[1187]	Less than 80% were ≥1 month to <36 months
Robertson et al. (2019)[1188]	Less than 80% were ≥1 month to <36 months
Robinson et al. (2000)[1189]	Less than 80% were ≥1 month to <36 months
Roland et al. (2019)[1190]	Less than 80% were ≥1 month to <36 months
Rosati et al. (2019)[1191]	Less than 80% were ≥1 month to <36 months
Rosenberg et al. (2017)[1192]	Less than 80% were ≥1 month to <36 months
Ross et al. (2020)[1193]	Less than 80% were ≥1 month to <36 months
Rossignol et al. (2009)[1194]	Age at treatment not reported
Roth et al. (2011)[1195]	Less than 80% were ≥1 month to <36 months
Roth et al. (2012)[1196]	Not a treatment of interest
Roth et al. (2014)[1197]	Less than 80% were ≥1 month to <36 months
Roulet-Perez et al. (2010)[1198]	N<10 surgery
Rubenstein et al. (2005)[1199]	Seizure type outside the scope (E.g., West syndrome, infantile spasms)
Rubinger et al. (2017)[1200]	Less than 80% were ≥1 month to <36 months
Rudebeck et al. (2018)[1201]	Less than 80% were ≥1 month to <36 months
Rufo-Campos et al. (2006)[1202]	Less than 80% were ≥1 month to <36 months
Ruiz-García et al. (2002)[1203]	Less than 80% were ≥1 month to <36 months
Ruiz Herrero et al. (2021)[1204]	Not in English
Russell et al. (2018)[1205]	No outcomes of interest
Russo et al. (2015)[1206]	Less than 80% were ≥1 month to <36 months
Russo et al. (2021)[1207]	Less than 80% were ≥1 month to <36 months
Russo et al. (2021)[1208]	N of 4-29 nonsurgery
Rychlicki et al. (2006)[1209]	Less than 80% were ≥1 month to <36 months
Rytter et al. (2009)[1210]	Less than 80% were ≥1 month to <36 months
Ryvlin et al. (2018)[1211]	Less than 80% were ≥1 month to <36 months
Saadeh et al. (2018)[1212]	Less than 80% were ≥1 month to <36 months
Sabaz et al. (2006)[1213]	Less than 80% were ≥1 month to <36 months
Sacino et al. (2017)[1214]	Less than 80% were ≥1 month to <36 months
Sadleir et al. (2020)[1215]	Less than 80% were ≥1 month to <36 months
Saffari et al. (2019)[1216]	N of 4-29 nonsurgery
Sahin et al. (2001)[1217]	Treatment to halt acute seizures (not prevention)
Sahin et al. (2003)[1218]	Treatment to halt acute seizures (not prevention)
Salpekar et al. (2020)[1219]	Not a treatment of interest

Study	Reason for Exclusion
Saltzman-Benaiah et al. (2003)[1220]	Less than 80% were ≥1 month to <36 months
Sampath et al. (2007)[1221]	Less than 80% were ≥1 month to <36 months
Samuel et al. (2019)[1222]	Less than 80% were ≥1 month to <36 months
Sánchez Fernández et al. (2015)[1223]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Sánchez Fernández et al. (2015)[1224]	No outcomes of interest
Sanchez et al. (2021)[1225]	N of 4-29 nonsurgery
Sandberg et al. (2005)[1226]	Less than 80% were ≥1 month to <36 months
Sands et al. (2016)[1227]	Neonates
Sands et al. (2019)[1228]	Less than 80% were ≥1 month to <36 months
Saneto et al. (2006)[1229]	Less than 80% were ≥1 month to <36 months
Sang et al. (2019)[1230]	Less than 80% were ≥1 month to <36 months
Sanmartí-Vilaplana et al. (2018)[1231]	Less than 80% were ≥1 month to <36 months
Sariego-Jamardo et al. (2015)[1232]	Age at treatment not reported
Sarkis et al. (2010)[1233]	Less than 80% were ≥1 month to <36 months
Sassower et al. (2001)[1234]	Less than 80% were ≥1 month to <36 months
Saxena et al. (2016)[1235]	Neonates
Scheffer et al. (2021)[1236]	Less than 80% were ≥1 month to <36 months
Scher et al. (2003)[1237]	Neonates
Schmeiser et al. (2016)[1238]	Less than 80% were ≥1 month to <36 months
Schmeiser et al. (2017)[1239]	Less than 80% were ≥1 month to <36 months
Schmitt et al. (2007)[1240]	Less than 80% were ≥1 month to <36 months
Schmitt et al. (2009)[1241]	Less than 80% were ≥1 month to <36 months
Scholtes et al. (2005)[1242]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Schulze-Bonhage et al. (2007)[1243]	Less than 80% were ≥1 month to <36 months
Sedighi et al. (2016)[1244]	Neonates
Seki et al. (2004)[1245]	Less than 80% were ≥1 month to <36 months
Selter et al. (2014)[1246]	Age at treatment not reported
Semprino et al. (2020)[1247]	No outcomes of interest
Seo et al. (2006)[1248]	Less than 80% were ≥1 month to <36 months
Seo et al. (2009)[1249]	Less than 80% were ≥1 month to <36 months
Shaabat et al. (2001)[1250]	Unable to obtain
Shah et al. (2019)[1251]	Less than 80% were ≥1 month to <36 months
Shahar et al. (2007)[1252]	N of 4-29 nonsurgery
Shahwan et al. (2009)[1253]	Less than 80% were ≥1 month to <36 months
Shain et al. (2013)[1254]	Less than 80% were ≥1 month to <36 months
Shakir et al. (2017)[1255]	No outcomes of interest
Sharma et al. (2009)[1256]	Less than 80% were ≥1 month to <36 months
Sharma et al. (2013)[1257]	Less than 80% were ≥1 month to <36 months
Sharma et al. (2016)[1258]	Less than 80% were ≥1 month to <36 months
Sharma et al. (2021)[1259]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Sharpe et al. (2008)[1260]	Less than 80% were ≥1 month to <36 months
Sharpe et al. (2020)[1261]	Neonates
Shehata et al. (2017)[1262]	Treatment to halt acute seizures (not prevention)
Sheinberg et al. (2015)[1263]	Less than 80% were ≥1 month to <36 months
Shen et al. (2018)[1264]	Less than 80% were ≥1 month to <36 months
Shepherd et al. (2017)[1265]	Less than 80% were ≥1 month to <36 months
Sherman et al. (2003)[1266]	Less than 80% were ≥1 month to <36 months
Sherman et al. (2008)[1267]	Less than 80% were ≥1 month to <36 months
Sheth et al. (2007)[1268]	Less than 80% were ≥1 month to <36 months
Shetty et al. (2016)[1269]	Less than 80% were ≥1 month to <36 months
Shi et al. (2016)[1270]	Age at treatment not reported
Shields et al. (2004)[1271]	Narrative review
Shim et al. (2008)[1272]	Less than 80% were ≥1 month to <36 months
Shim et al. (2008)[1273]	Case report (N=3 or fewer)
Shin et al. (2017)[1274]	Neonates
Shinnar et al. (2017)[1275]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Shirzadi et al. (2021)[1276]	Less than 80% were ≥1 month to <36 months
Shmuely et al. (2020)[1277]	Less than 80% were ≥1 month to <36 months
Shull et al. (2014)[1278]	N of 4-29 nonsurgery
Shurtleff et al. (2015)[1279]	Less than 80% were ≥1 month to <36 months
Sibilia et al. (2017)[1280]	Less than 80% were ≥1 month to <36 months
Siddiqui et al. (2021)[1281]	N<10 surgery
Sidebotham et al. (2015)[1282]	No denominator reported for age 1-36 months
Sierra-Marcos et al. (2017)[1283]	Less than 80% were ≥1 month to <36 months
Sigler et al. (2001)[1284]	Not a treatment of interest
Sillanp et al. (2009)[1285]	Less than 80% were ≥1 month to <36 months
Silva et al. (2006)[1286]	Less than 80% were ≥1 month to <36 months
Sinclair et al. (2003)[1287]	Less than 80% were ≥1 month to <36 months
Sinclair et al. (2003)[1288]	Case report (N=3 or fewer)
Sinclair et al. (2003)[1289]	Case report (N=3 or fewer)
Singhi et al. (2004)[1290]	Less than 80% were ≥1 month to <36 months
Sirén et al. (2007)[1291]	Less than 80% were ≥1 month to <36 months
Sivkova et al. (2011)[1292]	Not in English
Sivkova et al. (2013)[1293]	N of 4-29 nonsurgery
Skirrow et al. (2011)[1294]	Less than 80% were ≥1 month to <36 months
Skirrow et al. (2019)[1295]	Less than 80% were ≥1 month to <36 months
Skornicki et al. (2014)[1296]	Less than 80% were ≥1 month to <36 months
Slomski et al. (2017)[1297]	Comment/guideline/position statement/editorial
Smith et al. (2004)[1298]	Less than 80% were ≥1 month to <36 months
Smith et al. (2014)[1299]	Less than 80% were ≥1 month to <36 months
Sofou et al. (2017)[1300]	Less than 80% were ≥1 month to <36 months
Solanki et al. (2015)[1301]	Neonates
Soleman et al. (2018)[1302]	Less than 80% were ≥1 month to <36 months
Soleman et al. (2018)[1303]	Less than 80% were ≥1 month to <36 months
Søndergaard Khinchi et al. (2008)[1304]	Less than 80% were ≥1 month to <36 months
Sondhi et al. (2020)[1305]	Less than 80% were ≥1 month to <36 months
Song et al. (2018)[1306]	Less than 80% were ≥1 month to <36 months
Sonmez et al. (2013)[1307]	Less than 80% were ≥1 month to <36 months
Sotero de Menezes et al. (2001)[1308]	Less than 80% were ≥1 month to <36 months
Sottano et al. (2016)[1309]	Not in English
Souza-Oliveira et al. (2012)[1310]	Not in English
Spagnoli et al. (2016)[1311]	Neonates
Spilioti et al. (2016)[1312]	Less than 80% were ≥1 month to <36 months
Spuck et al. (2010)[1313]	Less than 80% were ≥1 month to <36 months
Spulber et al. (2009)[1314]	Less than 80% were ≥1 month to <36 months
Sreenivasan et al. (2011)[1315]	Less than 80% were ≥1 month to <36 months
Sridharan et al. (2020)[1316]	N of 4-29 non-surgery
Srikijvilaikul et al. (2018)[1317]	Less than 80% were ≥1 month to <36 months
Stainman et al. (2007)[1318]	Less than 80% were ≥1 month to <36 months
Steinborn et al. (2005)[1319]	Less than 80% were ≥1 month to <36 months
Stewart et al. (2019)[1320]	Less than 80% were ≥1 month to <36 months
Stigsdotter-Broman et al. (2014)[1321]	Less than 80% were ≥1 month to <36 months
Stromberg et al. (2021)[1322]	Less than 80% were ≥1 month to <36 months
Striano et al. (2007)[1323]	Less than 80% were ≥1 month to <36 months
Strzelczyk et al. (2019)[1324]	Less than 80% were ≥1 month to <36 months
Su et al. (2007)[1325]	Less than 80% were ≥1 month to <36 months
Sugano et al. (2014)[1326]	Less than 80% were ≥1 month to <36 months
Sullivan et al. (2020)[1327]	Less than 80% were ≥1 month to <36 months
Suman et al. (2017)[1328]	Less than 80% were ≥1 month to <36 months
Sun et al. (2015)[1329]	Less than 80% were ≥1 month to <36 months
Sunaga et al. (2009)[1330]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Suo et al. (2021)[1331]	Less than 80% were ≥1 month to <36 months
Suzuki et al. (2011)[1332]	Less than 80% were ≥1 month to <36 months
Sylvén et al. (2020)[1333]	Less than 80% were ≥1 month to <36 months
Szaflarski et al. (2018)[1334]	Less than 80% were ≥1 month to <36 months
Tacke et al. (2016)[1335]	Less than 80% were ≥1 month to <36 months
Tacke et al. (2018)[1336]	Less than 80% were ≥1 month to <36 months
Taghdiri et al. (2013)[1337]	Less than 80% were ≥1 month to <36 months
Taghdiri et al. (2015)[1338]	Less than 80% were ≥1 month to <36 months
Takeoka et al. (2001)[1339]	N of 4-29 nonsurgery
Takeoka et al. (2002)[1340]	N of 4-29 nonsurgery
Takeuchi et al. (2016)[1341]	Less than 80% were ≥1 month to <36 months
Tamilia et al. (2018)[1342]	Less than 80% were ≥1 month to <36 months
Tan et al. (2004)[1343]	Less than 80% were ≥1 month to <36 months
Tan et al. (2009)[1344]	Less than 80% were ≥1 month to <36 months
Tan et al. (2010)[1345]	Less than 80% were ≥1 month to <36 months
Tan et al. (2017)[1346]	Less than 80% were ≥1 month to <36 months
Tandon et al. (2009)[1347]	Less than 80% were ≥1 month to <36 months
Tang-Wai et al. (2017)[1348]	Less than 80% were ≥1 month to <36 months
Taraschenko et al. (2018)[1349]	Case report (N=3 or fewer)
Taub et al. (2014)[1350]	Less than 80% were ≥1 month to <36 months
Taylor et al. (1999)[1351]	Mean Age NR; does not seem to report outcome of interest
Tekgul et al. (2005)[1352]	Less than 80% were ≥1 month to <36 months
Tekgül et al. (2016)[1353]	Less than 80% were ≥1 month to <36 months
Tenney et al. (2014)[1354]	Case report (N=3 or fewer)
Tenney et al. (2018)[1355]	Less than 80% were ≥1 month to <36 months
Terra et al. (2010)[1356]	Less than 80% were ≥1 month to <36 months
Terra-Bustamante et al. (2005)[1357]	Less than 80% were ≥1 month to <36 months
Terra-Bustamante et al. (2005)[1358]	Less than 80% were ≥1 month to <36 months
Terra-Bustamante et al. (2007)[1359]	N<10 surgery
Terra-Bustamante et al. (2009)[1360]	Case report (N=3 or fewer)
Tetto et al. (2002)[1361]	Less than 80% were ≥1 month to <36 months
Teutonico et al. (2013)[1362]	Less than 80% were ≥1 month to <36 months
Thambi et al. (2021)[1363]	Less than 80% were ≥1 month to <36 months
Thammongkol et al. (2012)[1364]	Less than 80% were ≥1 month to <36 months
Thampratankul et al. (2015)[1365]	Less than 80% were ≥1 month to <36 months
Than et al. (2005)[1366]	Less than 80% were ≥1 month to <36 months
Thibault et al. (2020)[1367]	Neonates
Thiele et al. (2018)[1368]	Less than 80% were ≥1 month to <36 months
Thiele et al. (2019)[1369]	Less than 80% were ≥1 month to <36 months
Thiele et al. (2020)[1370]	Less than 80% were ≥1 month to <36 months
Thomas et al. (2010)[1371]	Less than 80% were ≥1 month to <36 months
Thomé-Souza et al. (2003)[1372]	Less than 80% were ≥1 month to <36 months
Thome-Souza et al. (2014)[1373]	Less than 80% were ≥1 month to <36 months
Thompson et al. (2012)[1374]	Less than 80% were ≥1 month to <36 months
Thudium et al. (2014)[1375]	Less than 80% were ≥1 month to <36 months
Tian et al. (2019)[1376]	N of 4-29 nonsurgery
Titre-Johnson et al. (2017)[1377]	Protocol
Titus et al. (2013)[1378]	Less than 80% were ≥1 month to <36 months
Toki et al. (2019)[1379]	Less than 80% were ≥1 month to <36 months
Tomlinson et al. (2017)[1380]	Less than 80% were ≥1 month to <36 months
Tomoum et al. (2008)[1381]	Less than 80% were ≥1 month to <36 months
Tomoum et al. (2009)[1382]	Less than 80% were ≥1 month to <36 months
Tomycz et al. (2018)[1383]	Not a treatment of interest
Tonekaboni et al. (2010)[1384]	Less than 80% were ≥1 month to <36 months
Tonekaboni et al. (2010)[1385]	Less than 80% were ≥1 month to <36 months
Topf et al. (2011)[1386]	Less than 80% were ≥1 month to <36 months
Toublanc et al. (2008)[1387]	No outcomes of interest
Trevathan et al. (2006)[1388]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Trezza et al. (2017)[1389]	Less than 80% were ≥1 month to <36 months
Tripathi et al. (2008)[1390]	Less than 80% were ≥1 month to <36 months
Tromp et al. (2003)[1391]	Less than 80% were ≥1 month to <36 months
Tsai et al. (1999)[1392]	Not a treatment of interest
Tsai et al. (2016)[1393]	Less than 80% were ≥1 month to <36 months
Tsai et al. (2020)[1394]	Less than 80% were ≥1 month to <36 months
Tsai et al. (2020)[1395]	Less than 80% were ≥1 month to <36 months
Tsuboyama et al. (2021)[1396]	No outcome data for any specific treatment
Turani et al. (2006)[1397]	Case report (N=3 or fewer)
Türkdogan et al. (2021)[1398]	Less than 80% were ≥1 month to <36 months
Tutor-Crespo et al. (2007)[1399]	Less than 80% were ≥1 month to <36 months
Tye et al. (2018)[1400]	Less than 80% were ≥1 month to <36 months
Tzadok et al. (2016)[1401]	Less than 80% were ≥1 month to <36 months
Ueda et al. (2021)[1402]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Ueshima et al. (2011)[1403]	No outcomes of interest
Ugras et al. (2006)[1404]	Less than 80% were ≥1 month to <36 months
Uldall et al. (1999)[1405]	Less than 80% were ≥1 month to <36 months
Uldall et al. (2000)[1406]	Less than 80% were ≥1 month to <36 months
Uliel-Sibony et al. (2020)[1407]	Less than 80% were ≥1 month to <36 months
Ünal et al. (2009)[1408]	Less than 80% were ≥1 month to <36 months
Ünalp et al. (2008)[1409]	Not a full paper (abstract only)
Ünalp et al. (2009)[1410]	Less than 80% were ≥1 month to <36 months
Underbjerg et al. (2015)[1411]	Less than 80% were ≥1 month to <36 months
Vachhrajani et al. (2012)[1412]	Less than 80% were ≥1 month to <36 months
Vadera et al. (2012)[1413]	Less than 80% were ≥1 month to <36 months
Vadera et al. (2012)[1414]	Less than 80% were ≥1 month to <36 months
Vaiman et al. (2017)[1415]	Less than 80% were ≥1 month to <36 months
Vaisleib et al. (2004)[1416]	Less than 80% were ≥1 month to <36 months
Valencia et al. (2009)[1417]	Less than 80% were ≥1 month to <36 months
Valova et al. (2020)[1418]	Less than 80% were ≥1 month to <36 months
Valvi et al. (2008)[1419]	Age at treatment not reported
van den Munckhof et al. (2018)[1420]	Treatment to halt acute seizures (not prevention)
van der Heide et al. (2012)[1421]	Neonates
van Der Louw et al. (2015)[1422]	N of 4-29 nonsurgery
van der Louw et al. (2019)[1423]	Less than 80% were ≥1 month to <36 months
van der Worp et al. (1999)[1424]	Narrative review
van Eeghen et al. (2012)[1425]	Less than 80% were ≥1 month to <36 months
van Empelen et al. (2004)[1426]	Case report (N=3 or fewer)
van Empelen et al. (2005)[1427]	Less than 80% were ≥1 month to <36 months
van Empelen et al. (2007)[1428]	Less than 80% were ≥1 month to <36 months
van Oijen et al. (2006)[1429]	Less than 80% were ≥1 month to <36 months
van Schooneveld et al. (2016)[1430]	Less than 80% were ≥1 month to <36 months
Vannicola et al. (2021)[1431]	N<10 surgery
Vargas et al. (2018)[1432]	Less than 80% were ≥1 month to <36 months
Vasquez et al. (2020)[1433]	Treatment to halt acute seizures (not prevention)
Vedantam et al. (2018)[1434]	Less than 80% were ≥1 month to <36 months
Veersema et al. (2019)[1435]	Less than 80% were ≥1 month to <36 months
Vega et al. (2015)[1436]	Less than 80% were ≥1 month to <36 months
Vehmeijer et al. (2015)[1437]	Less than 80% were ≥1 month to <36 months
Velaphi et al. (2013)[1438]	Neonates
Vendrame et al. (2007)[1439]	Less than 80% were ≥1 month to <36 months
Vendrame et al. (2010)[1440]	Less than 80% were ≥1 month to <36 months
Venkatesan et al. (2017)[1441]	Neonates
Verdian et al. (2010)[1442]	decision model
Verducci et al. (2019)[1443]	Less than 80% were ≥1 month to <36 months
Verhelst et al. (2005)[1444]	Less than 80% were ≥1 month to <36 months
Verrotti et al. (2001)[1445]	Less than 80% were ≥1 month to <36 months
Verrotti et al. (2002)[1446]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Verrotti et al. (2007)[1447]	Less than 80% were ≥1 month to <36 months
Verrotti et al. (2008)[1448]	Less than 80% were ≥1 month to <36 months
Verrotti et al. (2011)[1449]	Less than 80% were ≥1 month to <36 months
Verrotti et al. (2011)[1450]	Age at treatment not reported
Verrotti et al. (2013)[1451]	Less than 80% were ≥1 month to <36 months
Verrotti et al. (2013)[1452]	Age at treatment not reported
Verrotti et al. (2015)[1453]	N of 4-29 nonsurgery
Viggedal et al. (2012)[1454]	Less than 80% were ≥1 month to <36 months
Viggedal et al. (2013)[1455]	Less than 80% were ≥1 month to <36 months
Vigneswari et al. (2001)[1456]	Less than 80% were ≥1 month to <36 months
Vilaseca et al. (2000)[1457]	No outcomes of interest
Villaluz et al. (2018)[1458]	Less than 80% were ≥1 month to <36 months
Villarejo-Ortega et al. (2013)[1459]	Case report (N=3 or fewer)
Ville et al. (2002)[1460]	N of 4-29 nonsurgery
Villeneuve et al. (2009)[1461]	N of 4-29 nonsurgery
Virág et al. (2011)[1462]	Not in English
Visa-Reñé et al. (2020)[1463]	Less than 80% were ≥1 month to <36 months
Visudthibhan et al. (1999)[1464]	N<10 Surgery
Visudtibhan et al. (2001)[1465]	Study only states children <15 years old; no other information provided.
Volpon et al. (2020)[1466]	Less than 80% were ≥1 month to <36 months
Von der Brelie et al. (2014)[1467]	Less than 80% were ≥1 month to <36 months
Von Lehe et al. (2009)[1468]	Case report (N=3 or fewer)
Voronkova et al. (2007)[1469]	Only 12 in "early childhood," age not reported
Vossler et al. (2013)[1470]	Less than 80% were ≥1 month to <36 months
Voudris et al. (2004)[1471]	Less than 80% were ≥1 month to <36 months
Voudris et al. (2006)[1472]	Less than 80% were ≥1 month to <36 months
Voudris et al. (2006)[1473]	Less than 80% were ≥1 month to <36 months
Wagner et al. (2014)[1474]	Less than 80% were ≥1 month to <36 months
Wallander et al. (2014)[1475]	Less than 80% were ≥1 month to <36 months
Wang et al. (2014)[1476]	N<10 surgery
Wang et al. (2016)[1477]	Less than 80% were ≥1 month to <36 months
Wang et al. (2017)[1478]	Less than 80% were ≥1 month to <36 months
Wang et al. (2018)[1479]	Less than 80% were ≥1 month to <36 months
Wang et al. (2018)[1480]	Less than 80% were ≥1 month to <36 months
Wang et al. (2019)[1481]	Less than 80% were ≥1 month to <36 months
Wang et al. (2020)[1482]	Less than 80% were ≥1 month to <36 months
Wang et al. (2021)[1483]	Data unavailable
Weber et al. (2009)[1484]	Case report (N=3 or fewer)
Wehner et al. (2011)[1485]	Case report (N=3 or fewer)
Wei et al. (2014)[1486]	N of 4-29 nonsurgery
Weijenberg et al. (2018)[1487]	Less than 80% were ≥1 month to <36 months
Weil et al. (2015)[1488]	N<10 surgery
Weil et al. (2016)[1489]	Less than 80% were ≥1 month to <36 months
Weil et al. (2021)[1490]	Less than 80% were ≥1 month to <36 months
Weiner et al. (2006)[1491]	N<10 surgery
Weinstock et al. (2013)[1492]	N of 4-29 nonsurgery
Welin et al. (2017)[1493]	Data not specific to a treatment
Wellmer et al. (2012)[1494]	Less than 80% were ≥1 month to <36 months
Werner et al. (2007)[1495]	Less than 80% were ≥1 month to <36 months
Werth et al. (2006)[1496]	Less than 80% were ≥1 month to <36 months
Westerveld et al. (2000)[1497]	Less than 80% were ≥1 month to <36 months
Wheeler et al. (2021)[1498]	Less than 80% were ≥1 month to <36 months
Wheless et al. (2002)[1499]	Less than 80% were ≥1 month to <36 months
Wibisono et al. (2015)[1500]	Less than 80% were ≥1 month to <36 months
Wiemer-Kruel et al. (2017)[1501]	Less than 80% were ≥1 month to <36 months
Wijnen et al. (2017)[1502]	Less than 80% were ≥1 month to <36 months
Wilfong et al. (2005)[1503]	Less than 80% were ≥1 month to <36 months
Willems et al. (2021)[1504]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Williams et al. (2002)[1505]	Unable to obtain
Williams et al. (2002)[1506]	Less than 80% were ≥1 month to <36 months
Wilmshurst et al. (2005)[1507]	Narrative review
Wilmshurst et al. (2010)[1508]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Wirrell et al. (2001)[1509]	Age at treatment not reported
Wirrell et al. (2002)[1510]	Case report (N=3 or fewer)
Wirrell et al. (2008)[1511]	Less than 80% were ≥1 month to <36 months
Wirrell et al. (2013)[1512]	N<10 surgery
Wirrell et al. (2014)[1513]	Less than 80% were ≥1 month to <36 months
Wirrell et al. (2018)[1514]	N of 4-29 nonsurgery
Wohlrab et al. (1999)[1515]	Less than 80% were ≥1 month to <36 months
Worden et al. (2020)[1516]	Less than 80% were ≥1 month to <36 months
Wozniak et al. (2020)[1517]	Less than 80% were ≥1 month to <36 months
Wray et al. (2012)[1518]	Less than 80% were ≥1 month to <36 months
Wu et al. (2018)[1519]	Less than 80% were ≥1 month to <36 months
Wyllie et al. (2007)[1520]	Less than 80% were ≥1 month to <36 months
Xiao et al. (2014)[1521]	Less than 80% were ≥1 month to <36 months
Xie et al. (2017)[1522]	N of 4-29 nonsurgery
Xing et al. (2020)[1523]	Comment/guideline/position statement/editorial
Xu et al. (2002)[1524]	Not in English
Xu et al. (2007)[1525]	Less than 80% were ≥1 month to <36 months
Yamamoto et al. (2015)[1526]	Did not report outcomes of interest for the 1 age group in our scope
Yamamoto et al. (2015)[1527]	Less than 80% were ≥1 month to <36 months
Yamamoto et al. (2020)[1528]	Less than 80% were ≥1 month to <36 months
Yan et al. (2018)[1529]	N of 4-29 nonsurgery
Yang et al. (2002)[1530]	Not in English
Yang et al. (2009)[1531]	Less than 80% were ≥1 month to <36 months
Yang et al. (2010)[1532]	N of 4-29 nonsurgery
Yang et al. (2014)[1533]	Less than 80% were ≥1 month to <36 months
Yang et al. (2017)[1534]	Data not specific to a treatment
Yang et al. (2020)[1535]	No intervention (just describes patients)
Yeom et al. (2014)[1536]	Less than 80% were ≥1 month to <36 months
Yeung et al. (2000)[1537]	Less than 80% were ≥1 month to <36 months
Yildirim (2021)[1538]	Less than 80% were ≥1 month to <36 months
Yilmaz et al. (2014)[1539]	Less than 80% were ≥1 month to <36 months
Yilmaz et al. (2021)[1540]	Less than 80% were ≥1 month to <36 months
Yilmaz et al. (2021)[1541]	Less than 80% were ≥1 month to <36 months
Yis et al. (2009)[1542]	Less than 80% were ≥1 month to <36 months
You et al. (2008)[1543]	Less than 80% were ≥1 month to <36 months
You et al. (2008)[1544]	Less than 80% were ≥1 month to <36 months
Youn et al. (2020)[1545]	Less than 80% were ≥1 month to <36 months
Youness et al. (2020)[1546]	No intervention (only describes patients)
Yu et al. (2014)[1547]	Less than 80% were ≥1 month to <36 months
Yu et al. (2017)[1548]	Less than 80% were ≥1 month to <36 months
Yue et al. (2021)[1549]	Comment/guideline/position statement/editorial
Yukawa et al. (2000)[1550]	Less than 80% were ≥1 month to <36 months
Yüksel et al. (2000)[1551]	Less than 80% were ≥1 month to <36 months
Yum et al. (2013)[1552]	Seizure type outside the scope (e.g., West syndrome, infantile spasms)
Yun et al. (2011)[1553]	Less than 80% were ≥1 month to <36 months
Zaaimi et al. (2005)[1554]	Less than 80% were ≥1 month to <36 months
Zaaimi et al. (2007)[1555]	Less than 80% were ≥1 month to <36 months
Zaaimi et al. (2009)[1556]	Less than 80% were ≥1 month to <36 months
Zamani et al. (2014)[1557]	Less than 80% were ≥1 month to <36 months
Zamani et al. (2016)[1558]	Less than 80% were ≥1 month to <36 months
Zamponi et al. (2002)[1559]	Less than 80% were ≥1 month to <36 months
Zamponi et al. (2008)[1560]	N of 4-29 nonsurgery
Zamponi et al. (2010)[1561]	Less than 80% were ≥1 month to <36 months
Zamponi et al. (2011)[1562]	Less than 80% were ≥1 month to <36 months

Study	Reason for Exclusion
Zelnik et al. (2008)[1563]	Less than 80% were ≥1 month to <36 months
Zeng et al. (2012)[1564]	Less than 80% were ≥1 month to <36 months
Zhang et al. (2016)[1565]	Less than 80% were ≥1 month to <36 months
Zhang et al. (2018)[1566]	Less than 80% were ≥1 month to <36 months
Zhang et al. (2018)[1567]	Less than 80% were ≥1 month to <36 months
Zhang et al. (2019)[1568]	Less than 80% were ≥1 month to <36 months
Zhang et al. (2020)[1569]	Less than 80% were ≥1 month to <36 months
Zhang et al. (2020)[1570]	Less than 80% were ≥1 month to <36 months
Zhao et al. (2019)[1571]	Less than 80% were ≥1 month to <36 months
Zhao et al. (2021)[1572]	Less than 80% were ≥1 month to <36 months
Zhao et al. (2021)[1573]	Less than 80% were ≥1 month to <36 months
Zhou et al. (2019)[1574]	Less than 80% were ≥1 month to <36 months
Zhu et al. (2016)[1575]	Less than 80% were ≥1 month to <36 months
Zhu et al. (2018)[1576]	Less than 80% were ≥1 month to <36 months
Zilmer et al. (2021)[1577]	Less than 80% were ≥1 month to <36 months
Zubcevic et al. (2008)[1578]	Less than 80% were ≥1 month to <36 months
Zupanc et al. (2010)[1579]	Case report (N=3 or fewer)
Zupanc et al. (2010)[1580]	Less than 80% were ≥1 month to <36 months

Appendix C. Evidence Tables

Effectiveness (KQ1 and KQ2)

Pharmacologic Interventions

Table C-1. Effectiveness of pharmacologic interventions: Study characteristics

Study	Study Design	Country	Intervention(s)	N	Study Duration	Funding	Comments
Arzimanoglou et al. (2016)[1581]	Pre/Post	27 sites in Europe	Levetiracetam	101	Mean 5 months	UCB Pharma (manufacturer of the tested medication)	27 sites in Europe
Arican et al. (2018)[1582]	Pre/Post	Turkey	Levetiracetam	92	Median 12 months	No financial support received by authors	Izmir Katip Celebi University, Turkey
Grinspan et al. (2018)[1583]	Non-randomized comparative study	USA	Levetiracetam vs Phenobarbital	155	6 months	Pediatric Epilepsy Research Foundation	17 sites in the USA
Liu et al. (2020)[1584]	RCT	China	Valproate vs. Valproate + Levetiracetam	100	12 weeks	No financial support received by authors	Xiantao First People's Hospital Affiliated, China
Grosso et al. (2005)[1585]	Pre/Post	Italy	Topiramate	36	Median 11 months	NR	University of Siena, Italy
Kholin et al. (2014)[1586]	Pre/Post	Russia	Topiramate	58	NR, but 61% were on treatment for one year or more	NR	Pirogov Russian National Medical University, Russia
Kim et al. (2009)[1587]	Non-randomized comparative study	South Korea	Topiramate vs Carbamazepine	146	Mean 30.7 months	NR	Kyungpook National University Hospital, Daegu, South Korea

Study	Study Design	Country	Intervention(s)	N	Study Duration	Funding	Comments
Piña-Garza et al. (2008)[1588,1589]	Withdrawal RCT $	USA	Lamotrigine	204	At least 5 weeks initial open label phase; double blind phase 8 weeks; long-term open label 92% received the medication for at least 24 weeks	GlaxoSmithKline (the manufacturer of the study medication)	12 countries (USA, Australia, Estonia, France, Hungary, Italy, Latvia, Lithuania, The Netherlands, Portugal, Slovakia, Spain). While the study was designed as an RCT, the randomized portion of the study did not follow patients for at least 12 weeks, so for effectiveness data, we used the longer-term data reported by a secondary publication of the trial,[1589] which was a pre-post study.
Sicca et al. (2000)[1590]	Pre/Post	France	Phenytoin	55	3 months	NR	Hospital St. Vincent Du Paul, France
Jackson et al. (2017)[1591]	Pre/Post	USA	Vigabatrin	103	Average 12.1 months follow-up	Lundbeck Inc. (manufacturer of the tested medication)	Boston Children's Hospital, USA
Tanritanir et al. (2021)[1592]	Pre/Post	USA	Rufinamide	103	Median 15 months	Investigator initiated grant by Eisai Inc (manufacturer of the tested medication)	Boston Children's Hospital
Yamada et al. (2021)[1593]	Pre/Post	Japan	Stiripentol	95	2 years	Meiji Seika Pharma Co., Ltd	Throughout Japan

RCT = randomized controlled trial; NR: not reported

Table C-2. Effectiveness of pharmacologic interventions: Inclusion criteria

Study	Inclusion Criteria
Arican et al. (2018)[1582]	Diagnosed with epilepsy from January 2014 to January 2017, less than two years of age at the time levetiracetam was initiated as initial monotherapy and to be followed clinically for at least 6 months. Patients were excluded in the study if they had already received any other antiepileptic drug. Patients were also excluded when seizures had been caused by hypoglycemia and electrolyte disturbances such as hypocalcaemia or hypomagnesaemia.
Arzimanoglou et al. (2016)[1581]	Age 1-11 months diagnosed with epilepsy, received levetiracetam oral solution
Grinspan et al. (2018)[1583]	Diagnosed with nonsyndromic epilepsy at 1 of 17 U.S. pediatric epilepsy centers. Epilepsy was defined as 2 or more unprovoked seizures occurring on different days or a single seizure if the risk of recurrence was high enough to initiate treatment. Patients had to have nonsyndromic epilepsy and were aged 1 month to 1 year at the time of the first afebrile seizure. An infant was considered to have

Study	Inclusion Criteria
	nonsyndromic epilepsy if the treating pediatric neurologist determined the history was not consistent with electroclinical features of an infantile epilepsy syndrome. Excluded children who were not treated with an ASM during the year after the initial diagnosis of epilepsy began ASM polytherapy on the first day of treatment, started an ASM while awaiting surgery for a brain tumor, were unavailable for followup or died before 6 months, or had insufficient information in the database to determine whether a seizure had occurred in the period between 3 and 6 months after treatment initiation.
Liu et al. (2020)[1584]	Treated in Xiantao First People's Hospital Affiliated to Yangtze University (Xiantao, China) from December 2015 to 2018. Patients diagnosed with epilepsy based on the diagnosis criteria that conform to the epilepsy syndrome classification in 2014 National Standardized Diagnosis, Treatment and Scientific Research of Epilepsy, and they received no previous treatment and those without allergy history of medications used in this study. Exclusion criteria: Patients who recently took drugs that affect growth and development as well as glucose and lipid metabolisms, those who used glucocorticoids for a long time, those with severe electrolyte disorder, or those with severe dysfunctions of the liver or kidney
Grosso et al. (2005)[1585]	Affected by epilepsy and seen at the University of Siena from January 1999 to October 2003, aged less than 2 years, seizures refractory to at least 1 ASM.
Kholin et al. (2014)[1586]	Treated with topiramate for vital indications based on collective decisions of the team of physicians at the Pirogov Russian National Medical University, and at the Russian Pediatric Clinical Hospital, from 2002 to 2012.
Kim et al. (2009)[1587]	Under age 2 and initially prescribed either TPM or CBZ at the pediatric neurology clinic, Kyungpook National University Hospital, Daegu, South Korea from January 1, 2000, to December 31, 2003
Piña-Garza et al. (2008)[1588,1589]	Initial trial: Required at least a 40% reduction in seizures between the historical baseline phase and the last 4 weeks of the optimization period with lamotrigine to be randomly assigned to the double blind phase. Male or female infants aged 1 month (based on a 44-week conceptional age) to 24 months diagnosed with partial epilepsy uncontrolled by at least 1 ASM, had a history of at least 4 recurrent partial seizures (i.e., simple, complex, or evolving to secondarily generalized seizures) per month as extrapolated from a 1-week historic observation period immediately before initiation of study medication; had clinical laboratory values within normal limits at screening; had no underlying chronic metabolic abnormalities that could cause or confound the assessment of seizures; and, if they were on non-enzyme-inducing ASM at study entry, weighed at leas t6.7 kg. Exclusion criteria included diagnosis of severe, progressive myoclonus; presence of a progressive or unstable neurologic condition that had deteriorated during the month before study entry or seizures unrelated to epilepsy or resulting from drug withdrawal; use of felbamate, adrenocorticotropic hormone, previous use of lamotrigine, more than 2 ASMs as maintenance treatment, or valproate with at least 1 additional ASM at study entry; use of valproate for fewer than 6 months or, in the presence of hepatic dysfunction, for more than 6 months; having a functioning vagus nerve stimulator; or being on a ketogenic diet. Long-term followup: either had completed the open-label phase of the initial trial and parent/s guardians judged that continued use of lamotrigine might be beneficial, or were lamotrigine-naive patients who had partial seizures uncontrolled by 1-2 ASM and met the criteria for the initial trial.
Sicca et al. (2000)[1590]	Had been treated at Hospital St. Vincent Du Paul in the first 2 years of life between 1990 and 1997 with PHT for situation-related seizures or seizures occurring in the course of chronic epilepsy, and for whom sufficient data were available regarding clinical history, physical and neurological examinations, drug treatment, laboratory tests (hematology, blood chemistry, ASM plasma levels including PHT) and investigations (EEG, brain computed tomography, magnetic resonance imaging).
Jackson et al. (2017)[1591]	Diagnosed with epilepsy, electronic medical record available, treated with vigabatrin at Boston Children's over a 2-year period. Excluded patients whose vigabatrin initiation date was unavailable, whose baseline seizure frequency was unavailable, or whose followup seizure frequency was unavailable, or whose data were incomplete.
Tanritanir et al. (2021)[1592]	Age 36 months or fewer, received rufinamide for refractory epilepsy (at least 2 prior medications) between June 2010 and June 2018, and had “adequate” clinical information regarding seizure types, frequency, rufinamide dosing, and adverse events. Authors did not define “adequate.”

Study	Inclusion Criteria
Yamada et al. (2021)[1593]	Dravet syndrome, received stiripentol between November 2012 and July 2019, and visited the hospital at least once after stiripentol initiation. Authors reported a subgroup analyses of 95 infants age 0-2. To be included in analysis of responders, patients had to have at least 1 seizure during the 4-week baseline period and have sufficient data on seizure frequency during the assessments periods (did not define “sufficient”).

NR = not reported

Table C-3. Effectiveness of pharmacologic interventions: Intervention and patient characteristics

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior and Concurrent Treatments	Seizure Types
Arican et al. (2018)[1582]	Levetiracetam	Initially 10 mg/kg/day titrated up to 60 mg/kg/day. 26% ended at <30 mg/kg/day, 52% took 30-40 mg/kg/day, and the other 22% took >40 mg/kg/day.	92	52% female	NR	Median 6 months (IQR 1-10)	Structural 21%, metabolic 11%, genetic 9%, infectious 3%, unknown 56%	No other prior ASM. Those sufficiently controlled did not receive additional ASM. During the study, 31 patients were not sufficiently controlled and 30/31 received at least 1 of 11 additional ASM (% not reported).	Focal 58%, generalized 42%
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Mean daily dose 46 mg/kg/day (SD 16)	101	51% female	NR	Mean 6 months (SD 3)	Idiopathic focal 5%, temporal lobe epilepsy 12%, frontal lobe epilepsy 20%, occipital lobe epilepsy 5%, parietal lobe epilepsy 11%, Idiopathic generalized 7%, generalized benign neonatal familial convulsions 2%, generalized benign neonatal convulsions 1%, other generalized idiopathic 4%, West 19.8%, early infantile epileptic encephalopathy with suppression burst 1%, generalized symptomatic nonspecific etiology 1%, other	Prior ASM leveltiracetam 35%, phenobarbital 31%, vigabatrin 11%. Concomitant ASM during the study were vigabatrin 34%, phenobarbital 26%, valproate sodium 23%, and diazepam 20%.	25% focal simple, 43% focal complex, 34% partial evolving to secondary generalized, 1% generalized atypical absence, 8% generalized myoclonic, 7% generalized clonic , 21% generalized tonic, 17% generalized tonic clonic, 1% generalized atonic, 15% unclassified

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior and Concurrent Treatments	Seizure Types
							symptomatic generalized epilepsy 3%		
Grinspan et al. (2018)[1583]	Levetiracetam	First ASM prescribed by a neurologist, as monotherapy. No details of titration schedules. Median target dose 25 mg/kg/d	117	52% female	65% White, 29% Other, 6% Black	NR	All had nonsyndromic epilepsy. 60% unknown etiology, 17% developmental structural abnormality, 9% acquired etiology, 7% genetic etiology, 3% neurocutaneous etiology, 4% other.	No concomitant treatments were administered	Focal 56%, generalized 25%, mixed or unclear 19%
Grinspan et al. (2018)[1583]	Phenobarbital	First ASM prescribed by a neurologist, as monotherapy. No details of titration schedules. Median target dose 5 mg/kg/d	38	53% female	66% White, 29% Other, 5% Black	NR	All had nonsyndromic epilepsy. 42% unknown etiology, 32% developmental structural abnormality, 13% acquired etiology, 8% genetic etiology, 3% neurocutaneous etiology, 3% other.	No concomitant treatments were administered	Focal 61%, generalized 21%, mixed or unclear 18%
Liu et al. (2020)[1584]	Valproate	Initally 40 mg/kg/day and titrated to a maximum of 50 mg/kg/day, with 3 courses (30 days per course)	50	50% female	NR	2 years (SD 1.1)	NR	No prior treatments permitted. Did not report whether patients received concomitant treatments	NR
Liu et al. (2020)[1584]	Valproate + Levetiracetam	Valproate initally 40 mg/kg/day and titrated to	50	48% female	NR	2 years (SD 1.3)	NR	No prior treatments permitted. Did not report whether patients received	NR

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior and Concurrent Treatments	Seizure Types
		a maximum of 50 mg/kg/day, with 3 courses (30 days per course). Also received levetiracetam initially 20 mg/kg/day and increased once every 5-7 days to a maximum of 30 mg/kg/day.						concomitant treatments	
Grosso et al. (2005)[1585]	Topiramate	Mean dose 5.2 mg/kg/day	37	For the full N=59 enrolled: 47% female	NR	For the full N=59 enrolled: mean 13 months	For all 59 enrolled patients: post-anoxia ischemia 27%, brain malformation 10%, chromosome anomalies 7%, post-infectious 3%, progressive metabolic disorders 3%, cryptogenic 46%, idiopathic 3%	For all 59 enrolled patients: 37% were receiving 1 ASM before starting topiramate, 41% 2 ASM before starting topiramate, and 22% 3 ASM before starting topiramate. The other ASMs were valproate (58%), carbamazepine (41%), vigabatrin (37%), phenobarbital (24%), clonazepam (22%), lamotrigine (7%), and chlormeth-yldiazepam (5%)	For all 59 enrolled patients: Localization-related liiopathic early-onset occipital seizure 2%, localization related idiopathic benign partial complex seizure 2%, localization related cryptogenic 12%, localization related symptomatic 20%, localization related Bathing epilepsy 2%, generalized cryptogenic infantile spasms 10%,

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior and Concurrent Treatments	Seizure Types
									generalized symptomatic infantile spasms 22%, generalized symptomatic Ohtahara syndrome 2%, generalized symptomatic myoclonic epilepsy and MSNE 2%, generalized symptomatic others 3%, Dravet's syndrome 10%, unclassifiable 14%
Kholin et al. (2014)[1586]	Topiramate	No treatment details reported	58	48% female (based on the overall N=722)	NR	All < 1 year (no other information reported) for the data we extracted	Mixed (see list of 29 etiologies for the overall N=722 in Table 2 of the article). The 2 most common were symptomatic/cryptogenic frontal epilepsy (30%) and symptomatic/cryptogenic temporal epilepsy (22%).	For overall enrolled (N=722), 62% were using other ASM(s) in addition to topiramate (specific medications not reported)	NR
Kim et al. (2009)[1587]	Carbamazepine	Initial 5-10 mg/kg/day and increased weekly in increments of 5-10/mg/kg/day	105	46% female	NR	8.4 months (SD 5.6)	32% had presence of underlying pathology	No prior treatments permitted. Did not report whether patients received concomitant treatments.	44% partial, 47% generalized, 10% unclassified

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior and Concurrent Treatments	Seizure Types
		to a maximum of 30.							
Kim et al. (2009)[1587]	Topiramate	Initial 0.5-1 mg/kg/day and increased weekly in increments of 1/mg/kg/day to a maximum of 3-9.	41	54% female	NR	10 months (SD 6.4)	46% had presence of underlying pathology	No prior treatments permitted. Did not report whether patients received concomitant treatments.	20% partial, 71% generalized, 10% unclassified
Piña-Garza et al. (2008)[1588,1589]	Lamotrigine	Maximum maintenance dose 5.1 mg/kg/day for those on either valproate or a non-enzyme-inducing ASM, or 15.6 mg/kg/day for those on enzyme-inducing ASM.	204	44% female	84% White, 4%, Black, 7% American Hispanic, 1% Asian, 4% Other	Mean 15.9 months	NR	The concomitant ASM was enzyme-inducing in 59%, not enzyme-inducing in 30%, and was valproate in 11%.	Simple partial 27%, complex partial 62%, secondarily generalized 45%, generalized 25%, partial only 75%, generalized only 1%, both partial and generalized 23%
Piña-Garza et al. (2008)[1588,1589]	Replacement of lamotrigine with placebo	Withdrawal from Lamotrigine over an 8-week period whilebackground ASM were maintained.	19	53% female	89% White, 11% American Hispanic	Mean 14.2 months	NR	The concomitant ASM was enzyme-inducing in 74%, not enzyme-inducing in 26%	Simple partial 21%, complex partial 84%, secondarily generalized 32%, generalized 32%
Sicca et al. (2000)[1590]	Phenytoin	Oral treatment	55	For the full	NR	For the full N=82	For the full N=82 enrolled: Hypoxic-	Prior treatments not reported.	Generalized epilepsy 51%,

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior and Concurrent Treatments	Seizure Types
		(N=33 had started on long-term oral administration after intravenous PHT, and the other N=22 had received only oral administration).		N=82 enrolled: 51% female		enrolled: mean 7.4 months	ischaemic 13%, cortical dysplasia 10%, acute cerebral vasculopathy 9%, tuberous sclerosis 5%, meningitis 4%, viral encephalopathy 2%, multiple cerebral malformation 2%, peroxisomal disease 2%, mitochondrial encephalopathy 2%, other 11%, Not identified 39%	Concomitant treatments in 93%, most frequently vigabatrin, carbamazepine, clonazepam, clobazam, phenobarbital and valproate (did not report % of patients for each medication)	partial epilepsy 49%
Jackson et al. (2017)[1591]	Vigabatrin	Median dose at first followup was 100 mg/kg per day (IQR 79.4–125) and at last followup was 93.8 mg/kg per day (IQR 54-128.6).	103	53% female	NR	Mean 8 months (IQR 5-15)	Structural/metabolic 49.5%, TSC 24%, malformation of cortical development 18%, other 8%	Concomitant treatments were levetiracetam in 35%, topiramate in 31.1%, phenobarbital in 25.2%, clonazepam in 12.6%, clobazam in 10.7%, zonisamide in 9.7%, oxcarbazepine in 6.8%, valproic acid in 5.8%, phenytoin in 1.9%, rufinamide in 1.9%, lacosamide in 1.9%, lorazepam in 1.9%, lamotrigine in 0.97%, tiagabine in 0.97%, gabapentin in 0.97%, pyridoxine in 12%, steroid in	91% "epileptic spasm", 15% focal, 10% generalized tonic, 5% generalized myoclonic, 5% generalized tonic-clonic, 4% generalized atonic, and 1% generalized absence

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior and Concurrent Treatments	Seizure Types
								11%, ketogenic diet in 2%	
Tanritanir et al. (2021)[1592]	Rufinamide	50.5% started at 5 mg/kg/d, and the other 49.5% started at 10 mg/kg/d. Titration schedules varied. Median dosage at the last followup was 42 mg/kg/d (IQR 34-56).	103	42% female	NR	Median 20 months (IQR 13-28)	Structural brain / metabolic abnormality with identified genetic cause in 17 (16%), structural brain or metabolic abnormality with unidentified genetic cause in 33 (32%), unknown etiology in 35 (34%), and genetic cause in 19 (18%)	Levetiracetam 69%, Topiramate 39%, Clobazam 33%, Vigabatrin 32%, Clonazepam 20%, Phenobarbital 17%, ketogenic diet 16%, zonizamide 14%, valproic acid 10%, oxcarbazepine 7%, steroid 7%, lacosamide 5%, lamotrigine 5%, others 12%	Focal onset (22%), generalized tonic-clonic (23%), absence (10%), tonic (75%), myoclonic (43%), clonic (5%), atonic seizures (14%), epileptic spasms (64%) (and all patients had epilepsy).
Yamada et al. (2021)[1593]	Stiripentol	Not specifically reported for those age 0-2, but for the N=376 new patients, mean starting dose was 13.4 mg/kg/day. After 1 year, the mean dose was 32.5 mg/kg/day.	95	Not specifically reported for those age 0-2	100% Asian	Age range 0-2 years for the subgroup of interest	Not specifically reported for those age 0-2	Not specifically reported for those age 0-2, but for the N=376 new patients, 99% were taking sodium valproate, 93% were taking clobazam, 41% were taking bromide, and 41% were taking topiramate.	Not specifically reported for those age 0-2

IQR = interquartile range; NR = not reported

Table C-4. Effectiveness of pharmacologic interventions: Seizure outcomes

Study	Intervention	Specific Outcome Measurement	Timepoint	N	Result	Comments
Arican et al. (2018)[1582]	Levetiracetam	Seizure freedom	Median 12 months	92	66% (61/92)	None
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Epilepsy severity, marked improvement	Mean 5 months	85	33% (28/85)	Considers both seizure type and seizure frequency. 1-7 scale where 1=marked worsening and 7=marked improvement
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Epilepsy severity, moderate improvement	Mean 5 months	85	26% (22/85)	None
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Epilepsy severity, slight improvement	Mean 5 months	85	13% (11/85)	None
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Epilepsy severity, no change	Mean 5 months	85	19% (16/85)	None
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Epilepsy severity, slight worsening	Mean 5 months	85	2% (2/85)	None
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Epilepsy severity, moderate worsening	Mean 5 months	85	4% (3/85)	None
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Epilepsy severity, marked worsening	Mean 5 months	85	4% (3/85)	None
Liu et al. (2020)[1584]	Valproate	Seizure freedom	12 weeks	50	22% (11/50)	Table II
Liu et al. (2020)[1584]	Valproate + Levetiracetam	Seizure freedom	12 weeks	50	32% (16/50)	Table II
Liu et al. (2020)[1584]	Valproate	75%+ reduction	12 weeks	50	50% (25/50)	Table II
Liu et al. (2020)[1584]	Valproate + Levetiracetam	75%+ reduction	12 weeks	50	72% (36/50)	Table II
Liu et al. (2020)[1584]	Valproate	50%+ reduction	12 weeks	50	70% (35/50)	Table II
Liu et al. (2020)[1584]	Valproate + Levetiracetam	50%+ reduction	12 weeks	50	96% (48/50)	Table II
Grosso et al. (2005)[1585]	Topiramate	Seizure freedom	3 months	37	8% (3/37)	From Table 2, including only the N=37 patients without infantile spasm and providing data

Study	Intervention	Specific Outcome Measurement	Timepoint	N	Result	Comments
Grosso et al. (2005)[1585]	Topiramate	50%+ reduction	3 months	37	54% (20/37)	From Table 2, including only the N=37 patients without infantile spasm and providing data
Kholin et al. (2014)[1586]	Topiramate	Seizure freedom	NR	58	19% (11/58)	From Table 1
Kholin et al. (2014)[1586]	Topiramate	50% or more decrease in seizure frequency	NR	58	55% (32/58)	From Table 1
Kholin et al. (2014)[1586]	Topiramate	<50% change in seizure frequency	NR	58	34% (20/58)	From Table 1
Kholin et al. (2014)[1586]	Topiramate	Either a doubling of seizure frequency OR the appearance of new types of seizures	NR	58	10% (6/58)	From Table 1
Kim et al. (2009)[1587]	Carbamazepine	Seizure freedom	6 months	105	55% (58/105)	Estimated from Figure 3
Kim et al. (2009)[1587]	Topiramate	Seizure freedom	6 months	41	59% (24/41)	Estimated from Figure 3
Kim et al. (2009)[1587]	Carbamazepine	50%+ reduction	6 months	105	63% (66/105)	Estimated from Figure 3
Kim et al. (2009)[1587]	Topiramate	50%+ reduction	6 months	41	73% (30/41)	Estimated from Figure 3
Kim et al. (2009)[1587]	Carbamazepine	25%-50%+ reduction	6 months	105	4% (4/105)	Estimated from Figure 3
Kim et al. (2009)[1587]	Topiramate	25%-50%+ reduction	6 months	41	5% (2/41)	Estimated from Figure 3
Kim et al. (2009)[1587]	Carbamazepine	≤25% reduction	6 months	105	2% (2/105)	Estimated from Figure 3
Kim et al. (2009)[1587]	Topiramate	≤25% reduction	6 months	41	0% (0/41)	Estimated from Figure 3
Kim et al. (2009)[1587]	Carbamazepine	No improvement	6 months	105	24% (25/105)	Estimated from Figure 3
Kim et al. (2009)[1587]	Topiramate	No improvement	6 months	41	15% (6/41)	Estimated from Figure 3
Kim et al. (2009)[1587]	Carbamazepine	Worsening	6 months	105	8% (8/105)	Estimated from Figure 3
Kim et al. (2009)[1587]	Topiramate	Worsening	6 months	41	7% (3/41)	Estimated from Figure 3
Piña-Garza et al. (2008)[1588,1589]	Lamotrigine	Seizure freedom	≥24 weeks in 92%	204	13% (26/204)	None

Study	Intervention	Specific Outcome Measurement	Timepoint	N	Result	Comments
Piña-Garza et al. (2008)[1588,1589]	Lamotrigine	50%+ reduction	≥24 weeks in 92%	204	61% (124/204)	None
Piña-Garza et al. (2008)[1588,1589]	Lamotrigine	Increase in seizures by 26-49%	≥24 weeks in 92%	204	6% (12/204)	None
Piña-Garza et al. (2008)[1588,1589]	Lamotrigine	Increase in seizures by ≥50%	≥24 weeks in 92%	204	12% (24/204)	None
Piña-Garza et al. (2008)[1588,1589]	Lamotrigine	% reduction in seizures from baseline	≥24 weeks in 92%	204	Median 74% (SD: NR) (from a baseline mean of 21/week)	None
Sicca et al. (2000)[1590]	Phenytoin	Seizure freedom	3 months	55	4% (2/55)	None
Sicca et al. (2000)[1590]	Phenytoin	50%+ reduction	3 months	55	9% (5/55)	None
Jackson et al. (2017)[1591]	Vigabatrin	Seizure freedom	Median 12 months	88	38% (33/88)	Data is for last followup (first followup was <12 weeks)
Jackson et al. (2017)[1591]	Vigabatrin	50% or more decrease in seizure frequency	Median 12 months	88	73% (64/88)	Data is for last follow-up (first followup was <12 weeks)
Jackson et al. (2017)[1591]	Vigabatrin	% reduction in seizures from baseline	Median 12 months	88	Mean 97% (IQR 43.3% to 100%) (baseline NR)	None
Tanritanir et al. (2021)[1592]	Rufinamide	Median seizure frequency per 30 days (baseline 450 with an IQR or 150-900)	Median 15 months	103	Median seizure frequency per 30 days was 90 (IQR 5-540)	Corresponds to a 54% reduction in seizures (SD reported as 1175), p<0.0001 for the pre-post comparison
Tanritanir et al. (2021)[1592]	Rufinamide	Seizure freedom	Median 15 months	103	19% (20/103)	None
Tanritanir et al. (2021)[1592]	Rufinamide	50% or more reduction in seizure frequency	Median 15 months	103	50% (51/103)	None

Study	Intervention	Specific Outcome Measurement	Timepoint	N	Result	Comments
Tanritanir et al. (2021)[1592]	Rufinamide	Discontinuation due to lack of efficacy	Median 15 months	103	23% (24/103)	12 of the 24 discontinuations were due solely to lack of efficacy, and the other 12 were due to both adverse effects and lack of efficacy.

NR = not reported

Table C-5. Effectiveness of pharmacologic interventions: Other effectiveness outcomes

Study	Intervention	Specific Outcome Measurement	Timepoint	N	Result	Comments
Grinspan et al. (2018)[1583]	Levetiracetam	Freedom from monotherapy failure (no seizures during months 4-6 months after treatment initiation, AND no second ASM other than pyridoxine was prescribed during the full 6 months)	6 months	117	40% (47/117)	Unadjusted OR 3.6 (95% CI 1.5 to 10). Authors performed several additional analyses of these data, and all yielded the same conclusion that LEV was superior to PB. 1. Unadjusted analysis using generalized estimating equations OR 3.6 (95% CI 1.7 to 7.8). 2. Multivariable analysis with adjustment for age at onset, developmental delay, and time from seizure onset to first drug 3.1 (95% CI 1.3 to 7.4). 3. Propensity analysis, no adjustment for covariates, OR 4.2 (95% CI 1.1 to 16). 4. Propensity analysis, with adjustment for age at onset, developmental delay, and time from seizure onset to first drug, OR 4.2 (95% CI 1.3 to 14). 5. A variant of #3 above that excluded early failures, OR 4.8, (95% CI 1.3 to 18), and 6. a variant of #3 above that excluded those who failed monotherapy for reasons other than efficacy, OR=3.6 95% CI 1.2 to 11.
Grinspan et al. (2018)[1583]	Phenobarbital	Freedom from monotherapy failure (no seizures during months 4-6 months after treatment initiation, AND no second ASM other than pyridoxine was prescribed during the full 6 months)	6 months	38	16% (6/38)	None
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Psychomotor development, marked improvement	Mean 5 months	85	19% (16/85)	1-7 scale where 1=marked worsening and 7=marked improvement

Study	Intervention	Specific Outcome Measurement	Timepoint	N	Result	Comments
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Psychomotor development, moderate improvement	Mean 5 months	85	13% (11/85)	None
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Psychomotor development, slight improvement	Mean 5 months	85	21% (18/85)	None
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Psychomotor development, no change	Mean 5 months	85	36% (31/85)	None
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Psychomotor development, slight worsening	Mean 5 months	85	4% (3/85)	None
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Psychomotor development, moderate worsening	Mean 5 months	85	4% (3/85)	None
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Psychomotor development, marked worsening	Mean 5 months	85	4% (3/85)	None
Liu et al. (2020)[1584]	Valproate	Mini-Mental State Examination (MMSE) scale (range 0-100 where higher scores are better)	12 weeks	50	Mean 71.7 (SD: 2.3) (baseline NR)	Table IV. Reported as statistically significantly superior in the VAL+LEV group
Liu et al. (2020)[1584]	Valproate	Wechsler Memory Scale-Revised in China (WMS-RC) (range 0-100 where higher scores are better)	12 weeks	50	Mean 78.4 (SD: 2.4) (baseline NR)	Table IV. Reported as statistically significantly superior in the VAL+LEV group
Liu et al. (2020)[1584]	Valproate + Levetiracetam	MMSE scale (range 0-100 where higher scores are better)	12 weeks	50	Mean 89.5 (SD: 2.1) (baseline NR)	Table IV. Reported as statistically significantly superior in the VAL+LEV group
Liu et al. (2020)[1584]	Valproate + Levetiracetam	WMS-RC (range 0-100 where higher scores are better)	12 weeks	50	Mean 90.8 (SD: 2.6) (baseline NR)	Table IV. Reported as statistically significantly superior in the VAL+LEV group
Liu et al. (2020)[1584]	Valproate	Montreal cognitive assessment (MoCA) scale (scale range 0-30 where higher numbers are better)	12 weeks	50	Mean 21.5 (SD: 1.9) (baseline NR)	Table IV. Reported as statistically significantly superior in the VAL+LEV group

Study	Intervention	Specific Outcome Measurement	Timepoint	N	Result	Comments
Liu et al. (2020)[1584]	Valproate + Levetiracetam	MoCA scale (scale range 0-30 where higher numbers are better)	12 weeks	50	Mean 27.9 (SD: 2) (baseline NR)	Table IV. Reported as statistically significantly superior in the VAL+LEV group
Liu et al. (2020)[1584]	Valproate	Daily living abilities, Barthel Index (range 0-100 where higher scores are better)	12 weeks	50	Mean 62 (SD: 3) (baseline NR)	Estimated from Figure 1. Reported as statistically significantly superior in the VAL+LEV group
Liu et al. (2020)[1584]	Valproate + Levetiracetam	Daily living abilities, Barthel Index (range 0-100 where higher scores are better)	12 weeks	50	Mean 86 (SD: 1) (baseline NR)	Estimated from Figure 1. Reported as statistically significantly superior in the VAL+LEV group
Liu et al. (2020)[1584]	Valproate	QOL in epilepsy-31 inventory (QOLIE-31) scale revised for Chinese patients (range 0-100 where higher scores are better)	12 weeks	50	Mean 60 (SD: 5) (baseline NR)	Estimated from Figure 1. Reported as statistically significantly superior in the VAL+LEV group
Liu et al. (2020)[1584]	Valproate + Levetiracetam	QOL in epilepsy-31 inventory (QOLIE-31) scale revised for Chinese patients (range 0-100 where higher scores are better)	12 weeks	50	Mean 84 (SD: 1) (baseline NR)	Estimated from Figure 1. Reported as statistically significantly superior in the VAL+LEV group
Yamada et al. (2021)[1593]	Stiripentol	“Marked” or “Moderate” improvement	Two years	92	54% (50/92)	Physicians rated improvement on a 1-5 scale where 1=marked, 2=moderate, 3=mild, 4=no change, 5=worsened. This was based on seizure frequency, duration, intensity, and the ability to undertake activities of daily living.

NR = not reported

Table C-6. Pharmacologic intervention: Risk of bias of RCTs

Trial and Outcome	Generation f Randomization	Allocation Concealment	Baseline Imbalance	Patient Blinded	Staff Blinded	Differential Ancillary Treatments	Adherence	Analytic approach to address departures from	Data On At Least 80% of those Enrolled	Differential Dropout <=15%	Standard Way To Measure The Outcome	Blinded Outcome Assessor	Bias In Selection Of Reported Results	Overall Risk of Bias
Liu et al. (2020)[1584] Seizure freedom	SC	SC	SC	Low	SC	SC	SC	SC	Low	Low	Low	SC	Low	**High**
Liu et al. (2020)[1584] Quality of life	SC	SC	SC	Low	SC	SC	SC	SC	Low	Low	Low	SC	Low	**High**
Novotny et al. (2010)[1594,1595] Adverse events	Low	Low	Low	Low	Low	SC	Low	Low	Low	Low	Low	Low	Low	**Low**
Manitpisitkul et al. (2013)[1596] Adverse events	Low	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	High	Low	**Moderate**
Liu et al. (2020)[1584] Adverse events	SC	SC	SC	Low	SC	SC	SC	SC	Low	Low	Low	SC	SC	**High**
Piña-Garza et al. (2008)[1588,1589] Adverse events	SC	SC	SC	Low	Low	Low	SC	Low	Low	Low	Low	Low	Low	**Moderate**

We only rated risk of bias for studies for which we rated the strength of evidence (SOE). Other studies are discussed in the text.
SC = Some concerns

Table C-7. Pharmacologic interventions: Risk of bias of controlled nonrandomized comparative studies

Study and Outcomes	Confounding†	Selection Into Study	Classification Of Interventions	Differential Ancillary Treatments	Adherence	Data On At :east 80% Of Those Enrolled	Differential Dropout <=15%	Standard Way To Measure The Outcome	Blinded Outcome Assessor	Bias In Selection Of Reported Result	Overall Risk Of Bias
Kim et al. (2009)[1587] Seizure freedom, adverse events	High	SC	Low	SC	SC	Low	Low	Low	SC	Low	**High**

We only rated risk of bias for studies for which we rated the strength of evidence (SOE). Other studies are discussed in the text.

SC = Some concerns

† Studies were required to report baseline seizure frequency and number of prior antiseizure medications (ASM)

Table C-8. Pharmacologic interventions: Risk of bias of pre/post studies

Study and Outcome	Item 1†	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Overall Risk of Bias
Arican et al. (2018)[1582] Seizure freedom	SC	Low	Low	Low	High	Low	SC	Low	High	**High**
Arican et al. (2018)[1582] Adverse events	High	High	Low	Low	High	Low	SC	SC	High	**High**
Arzimanoglou et al. (2016)[1581] Adverse events	High	High	SC	Low	High	Low	Low	Low	SC	**High**
Grosso et al. (2005)[1585] Seizure freedom	SC	High	SC	Low	High	Low	Low	Low	SC	**High**
Kholin et al. (2014)[1586] Seizure freedom	High	High	Low	Low	High	Low	SC	SC	High	**High**
Kim et al. (2010)[1597] Adverse events	Low	High	Low	Low	High	Low	SC	SC	High	**High**
Piña-Garza et al. (2008)[1588,1589] Seizure frequency	SC	High	Low	Low	High	Low	Low	SC	SC	**High**
Piña-Garza et al. (2008)[1588,1589] Seizure freedom	SC	High	Low	Low	High	Low	Low	SC	SC	**High**
Piña-Garza et al. (2008)[1588,1589] Adverse events	High	High	Low	Low	High	Low	Low	SC	SC	**High**
Sicca et al. (2000)[1590] Seizure freedom	High	High	Low	Low	High	Low	SC	SC	High	**High**
Sicca et al. (2000)[1590] Adverse events	High	High	Low	Low	High	Low	SC	SC	High	**High**
Jackson et al. (2017)[1591] Seizure frequency	SC	High	Low	Low	High	Low	SC	Low	High	**High**
Jackson et al. (2017)[1591] Seizure freedom	SC	High	Low	Low	High	Low	SC	Low	High	**High**

Study and Outcome	Item 1†	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Overall Risk of Bias
Jackson et al. (2017)[1591] Adverse events	High	High	Low	Low	High	Low	SC	Low	High	**High**
Tanritanir et al. (2021)[1592] Seizure freedom	SC	High	Low	Low	High	Low	Low	Low	High	High
Tanritanir et al. (2021)[1592] Seizure frequency	SC	High	Low	Low	High	Low	Low	Low	High	High
Tanritanir et al. (2021)[1592] Adverse events	High	High	Low	Low	High	Low	Low	Low	High	High
Yamada et al. (2021)[1593] Adverse events	High	High	Low	Low	High	Low	SC	High	High	High

We rated risk of bias only for studies for which we rated the strength of evidence (SOE). Other studies are discussed in the text.
Risk of bias items for Pre/Post studies
1 Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
2 Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
3 Did the study maintain fidelity to the intervention protocol?
4 If attrition (overall or differential nonresponse, dropout, loss to followup, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?
5 Were the outcome assessors blinded to the intervention or exposure status of participants?
6 Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?
7 Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?
8 Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?
9 Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?
SC = Some concerns

Dietary Interventions

Table C-9. Dietary interventions: Study characteristics

Study	Study Design	Country	Interventions	n	Comparator	n	Study Duration	Funding	Comments
Suo et al. 2012[1598]	Pre/Post	China	Ketogenic Diet (classic)	147	NA	NA	12 months	NR	Conducted at Shenzhen Children's Hospital.

Study	Study Design	Country	Interventions	n	Comparator	n	Study Duration	Funding	Comments
Wu et al. 2015[1599]	Pre/Post	China	Ketogenic diet (classic)	40	NA	NA	6 months	6 Major Human Resources Project of Jiangsu Province	Conducted at Children's Hospital of Fudan University.
Kim et al. 2019[1600]	Pre/Post	USA	Ketogenic diet	49	NA	NA	3 months	None	Conducted at Lurie Children's Hospital. Patients with West Syndrome excluded per protocol.
Dressler et al. 2015[355]	Pre/Post	Austria	Ketogenic diet (classic)	58	NA	NA	18 months	None	Conducted at Medical University Vienna.
Kang et al. 2005[1601]	Pre/Post	Korea	Ketogenic diet (classic)	49	NA	NA	12 months	NR	Conducted at Epilepsy Centers in Yonsei University and Inje University.
Liu et al. 2021[1602]	Pre/Post	China	Ketogenic diet (classic)	41	NA	NA	12 months	NR	Conducted at Children's Hospital of Chongqing Medical University, Chongqing, China.
El-Rashidy et al. 2013[1603]	RCT	Egypt	Ketogenic diet (classic)	10	Modified Atkins diet ASM Polytherapy	15 15	> 6 months	Children's hospital, Faculty of Medicine, Ain Shams University	Conducted at Children's Hospital Ain Shams University
Kim et al. 2015[1604]	RCT	Korea	Ketogenic diet (classic)	17	Modified Atkins diet	20	6 months	National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology	Conducted at Severance Hospital

NA = not applicable; NR = not reported; ASM = antiseizure medication

Table C-10. Dietary interventions: Patient characteristics

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments
Suo et al. 2012[1598]	Intractable epilepsy, previously on 3 anticonvulsant but still had more than 4 seizures a week. Known metabolic disorders or severe systemic illnesses excluded.	Ketogenic diet (classic)	147	NRFS Total population, including any age: 206 males 111 females	0 to 2 years old.	NRFS Total population, including any age: 157 infantile spasms	At least 3 anticonvulsants
Wu et al. 2015[1599]	Prior exposure to the appropriate use of at least 2 anticonvulsants without any other antiepileptic treatments such as resective surgery or implantation of a neurostimulation device and seizure frequency of at least 1 per week. Inherited metabolic diseases, liver and urinary calculikidney dysfunction, hyperlipidemia, urinary calculi excluded.	Ketogenic diet (classic)	40	NRFS Total population, including any age: 62 males 25 females	0 to 1 year: 6 1 to 3 years: 34	NRFS Total population, including any age: 31 spasms, 2 tonic, 6 tonic–clonic, 6 myoclonic, 1 atonic, 4 partial seizure, 20 LGS, 5 Dravet, 6 Doose, 2 LKS	At least 2 anticonvulsants
Kim et al. 2019[1600]	Under the age of 3 years with medically intractable epilepsy, defined as persistent seizures despite the use of two or more appropriate anticonvulsants at therapeutic doses.	Ketogenic diet	49	NRFS Total population, including any age: 50 males 59 females	Mean 1.4 ± 0.8	Non West syndrome	Median 4 anticonvulsants
Dressler et al. 2015[355]	Included were all children with complete clinical data and observation periods of at least 3 months after initiation of the KD.	Ketogenic diet (classic)	58	NRFS Total population, including any age: 56 males 59 females	0.68 ± 0.45 years	NRFS Total population, including any age: 18 genetic, 54 structural/metabolic, 43 unknown	2.47 ± 2 ASM

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments
Kang et al. 2005[1601]	Patients who had been experiencing more than four seizures per month and uncontrolled by the initial combination of three or more ASM.	Ketogenic diet (classic)	49	NRFS Total population, including any age: 110 males 89 females	< 2 years	NRFS Total population, including any age: 39 infantile spasms, 16 myoclonic, 28 atonic, 16 generalized tonic-clonic, 14 generalized tonic, 16 SMEI, 4 LKS, 2 EIEE, 9 nonspecific generalized seizure, 54 nonspecific partial seizure	3.14 ASM
Liu et al. 2021[1602]	Infants born full terms aged 6 to 36 months with refractory epilepsy who took 2 or more anticonvulsants. Patients with organ failures, chronic infectious diseases, or thyroid disorders were excluded.	Ketogenic diet (classic)	•41	23 males 18 females	•20.51 ± 4.05 months	NR	2 or more anticonvulsants
El-Rashidy et al. 2013[1603]	Patients diagnosed with symptomatic intractable epilepsy according to the definition of Beleza.	• Ketogenic diet (classic) • Modified Atkins diet • Normal diet	•10 •15 •15	•5 males 5 females •8 males 7 females •8 males 7 females	•26 ± 0.9 months •27.13 ± 6.63 months •25.73 ± 6.35 months	•11 post-anoxic, 3 post-traumatic, 7 post-hemorrhagic. 3 focal, 4 general, 2 infantile spasm, 1 early infantile myoclonic encephalopathy. •3 post-anoxic, 4 post-hemorrhagic, 2 Tuberous sclerosis, 1 syndromic epilepsy. 4 focal, 11 general.	ASM polytherapy for all

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments
Kim et al. 2015[1604]	Patient age 1–18 years, seizure frequency >4 per month, and treatment failure of ≥2 prescribed ASM.	• Ketogenic diet (classical) • Modified Atkins diet	•17 •20	Total KD population, including any age: 32 males 19 females Total MAD population, including any age: 26 males 27 females	•1 to 2 years •1 to 2 years	NRFS Total Ketogenic diet population, including any age: 8 tonic, 4 tonic-clonic, 4 myoclonic. 2 atonic, 12 epileptic spasms, 21 focal, 10 LGS, 8 West, 1 MAE, 2 Dravet, 30 epilepsy unspecified Total MAD population, including any age: 9 tonic, 2 tonic-clonic, 3 myoclonic. 1 atonic, 16 epileptic spasms, 21 focal, 8 LGS, 12 West, 1 MAE, 4 Dravet 28 epilepsy unspecified	≥2 prescribed antiepileptic drugs

ASM = antiseizure medications; IQR = interquartile range; LGS = Lennox Gastaut Syndrome; MAE = Myoclonic astatic epilepsy; NA = not applicable; NR = not reported; NRFS = not reported for the subgroup;

Table C-11. Dietary interventions: Treatment characteristics

Study	Intervention	n	Treatment Details	Seizure Measurement Methods	Comments
Suo et al. 2012[1598]	Ketogenic diet (classic)	147	Johns Hopkins Hospital protocol with an initial fasting stage of about 24 h, and a diet lipid-to-nonlipid ratio of 4:1.	Parental report and seizure diaries	None
Wu et al. 2015[1599]	Ketogenic diet (classic)	40	4:1 ratio of fat:protein plus carbohydrates) using a KD vegetable protein beverage (Ketogenicsz)	Parental daily seizure calendars	None

Study	Intervention	n	Treatment Details	Seizure Measurement Methods	Comments
Kim et al. 2019[1600]	Ketogenic diet	49	KD was initiated at a ratio of 1:1 (fat grams: carbohydrate + protein grams) without a fast as an inpatient in the hospital. The keto ratio was increased daily, reaching up to 3:1 on day 3. On day 4, patients were discharged home at the ratio of 3:1 with full calories. Fluids were not restricted.	Medical records, retrospective study.	None
Dressler et al. 2015[355]	Ketogenic diet (classic)	58	According to the Johns Hopkins protocol without fasting and fluid restriction. The ketogenic ratio in infants during the first year of life is usually 3:1 or 2.5:1. In older children the ketogenic ratio used is 4:1.	Parental seizure diaries and EEG	None
Kang et al. 2005[1601]	Ketogenic diet (classic)	49	Johns Hopkins Protocol	Medical records and seizure diaries	None
Liu et al. 2021[1602]	Ketogenic diet (classic)	41	Classic KD, unspecified.	NR	None
El-Rashidy et al. 2013[1603]	• Ketogenic diet (classic) • Modified Atkins diet • Normal diet	•10 •15 •15	•The classic 4:1 KD was provided by as a formula. •Modified Atkins diet consisted of a nearly balanced diet (60% fat, 30% protein, and 10% carbohydrates by weight) without restrictions. •Normal accustomed diet with anti-epileptic polytherapy.	Seizure frequency and severity recorded during outpatient visits, details not specified.	All groups concurrently on ASM: valproic acid and carbamazepine ± clonazepam
Kim et al. 2015[1604]	• Ketogenic diet (classic) • Modified Atkins diet	•17 •20	•4:1 lipid to nonlipid ratio and nonfasting initiation protocol. •Johns Hopkins Protocol.	Seizure diaries.	None

ASM = Antiseizure medications; EEG = Electroencephalography; NR=Not reported

Table C-12. Dietary interventions: Seizure outcomes

Study	Intervention	Baseline	Seizure Outcomes	Hospitalization, Mortality, SUDEP	Comments
Suo et al. 2012[1598]	Ketogenic diet (classic)	NRFS	Seizure free at 12 months: 17 of 147 (11.6%) Reduction 90-99%: 3 (2.0%) Reduction 50-90%: 7 (4.8%) Reduction <50%: 2 (1.4%) No change: 4 (2.7%) Drop out: 114 (77.6%)	NR	147 started diet; 114 dropped out; only 33 remained on the diet at 12 months. Data taken from Table 3.
Wu et al. 2015[1599]	Ketogenic diet (classic)	NRFS	**3 months:** Seizure free: 10 (25%) >90% reduction: 3 (7.5%) 50-90% reduction: 6 (15%) <50% reduction: 21 (52.5%) Effective: 13 (32.5%) Ineffective: 27 (67.5%) **6 months:** Seizure free: 13 (32.5%) >90% reduction: 2 (5%) 50-90% reduction: 6 (15%) <50% reduction: 19 (47.5%)	NR	Subgroup of <1 year not extracted due to low patient count (n=6).
Kim et al. 2019[1600]	Ketogenic diet	NRFS	**3 months:** Responder: >50% reduction: 18 Nonresponder:<50% reduction: 31	NR	None

Study	Intervention	Baseline	Seizure Outcomes	Hospitalization, Mortality, SUDEP	Comments
Dressler et al. 2015[355]	Ketogenic diet (classic)	NR	**3 months:** Responders: 37 (63.8%) Seizure Free: 20 (34.5%) **6 months:** Responders: 32 (55.2%) Seizure Free: 19 (32.7%) **12 months:** Responders: 27 (84.3%)* Seizure Free: 19 (70.4%)* **6 months after KD:** Responders: 21 (42.9%) Seizure Free: 15 (30.6%)	NR	Article reports conflicting data.
Kang et al. 2005[1601]	Ketogenic diet (classic)	NR	**3 months:** >50% reduction: 28/49 Seizure free: 16/49 **6 months:** >50% reduction: 27/49 Seizure free: 18/49 **12 months:** >50% reduction: 16/49 Seizure free: 13/49	NR	>50% reduction includes seizure free patients.

Liu et al. 2021[1602]	Ketogenic diet (classical)	NR	**Ketogenic Diet (classic):**
			• 3 months:
			  ○ 90% to 99% reduction: 7
			  ○ 50% to 90% reduction: 21
			  ○ <50% reduction: 13
			• 6 months:
			  ○ 90% to 99% reduction: 8
			  ○ 50% to 90% reduction: 24
			  ○ <50% reduction: 9
			• 12 months:
			  ○ 90% to 99% reduction: 9
			  ○ 50% to 90% reduction: 25
			  ○ <50% reduction: 7
				NR	None

Study	Intervention	Baseline	Seizure Outcomes	Hospitalization, Mortality, SUDEP	Comments
El-Rashidy et al. 2013[1603]	• Ketogenic diet (classic) • Modified Atkins diet • Normal diet	NR	**Ketogenic Diet (classic)** • 3 months: ○ Frequency change: -57.95±17.73 ○ Chalfont score change: -31.95±18.71 • 6 months: ○ Frequency change: -70.79±19.26 ○ Chalfont score change: -35.89±19.40 **Modified Atkins Diet** • 3 months: ○ Frequency change: -7.04±12.68 ○ Chalfont score change: -16.03±7.06 • 6 months: ○ Frequency change: -28.03±21.39 ○ Chalfont score change: -37.63±4.75 **Normal Diet (polytherapy)** • 3 months: ○ Frequency change: 6.22±34.41 ○ Chalfont score change: -0.45±4.91 • 6 months: ○ Frequency change: -8.31±46.81 ○ Chalfont score change: -1.79±7.94	NR	None

Study	Intervention	Baseline	Seizure Outcomes	Hospitalization, Mortality, SUDEP	Comments
Kim et al. 2015[1604]	• Ketogenic diet (classic) • Modified Atkins diet	NR	**Ketogenic Diet (classic)** • 3 months: ○ Seizure frequency: mean 19.21% of baseline. ○ Seizure frequency: Seizure free: 9 of 17 (53%) >90% reduction: 9 >50% reduction: 10 • 6 months: ○ Seizure frequency: mean 0% of baseline. ○ Seizure frequency: Seizure free: 9 of 17 (53%) >90% reduction: 10 >50% reduction: 10 **Modified Atkins Diet** • 3 months: ○ Seizure frequency: mean 46.18% of baseline. ○ Seizure frequency: Seizure free: 4 of 20 (20%) >90% reduction: 5 >50% reduction: 8 • 6 months: ○ Seizure frequency: mean 39.76% of baseline. ○ Seizure frequency: Seizure free: 5 of 20 (25%) >90% reduction: 7 >50% reduction: 9	NR	No baseline value reported. Data from Table 3 from children age 1 to <2 years old.

NA = not applicable; NR = not reported; NRFS = not reported for the subgroup; KD = ketogenic diet

Table C-13. Dietary interventions: Risk of bias of RCTs

RCTs	Outcome	Generation f Randomization sequence	Allocation Concealment	Baseline Imbalance	Patient Blinded	Staff Blinded	Differential Ancillary Treatments	Adherence	Analytic approach to address departures from intended intervention	Data On At Least 80% of those Enrolled	Differential Dropout <=15%	Standard Way To Measure The Outcome	Blinded Outcome Assessor	Bias In Selection Of Reported Results	Overall Risk of Bias
El-Rashidy et al. 2013[1603]	Seizure frequency	SC	High	High	Low	High	SC	SC	Low	Low	Low	Low	High	Low	High
El-Rashidy et al. 2013[1603]	Adverse events	SC	High	High	Low	High	SC	SC	Low	Low	Low	Low	High	Low	High
Kim et al. 2015[1604]	Seizure frequency	Low	High	Low	Low	SC	SC	SC	Low	SC	SC	SC	High	Low	High
Kim et al. 2015[1604]	Seizure freedom	Low	High	Low	Low	SC	SC	SC	Low	SC	SC	Low	High	Low	High

Table C-14. Dietary interventions: Risk of bias of pre/post studies

Pre/Post	Outcome	Study Addressed Ootential Confounding†	Study Ruled Out Any Impact From Concurrent Intervention or exposure	Fidelity To Intervention Protocol	Bias Due To Attrition	Outcome Assessor Blinding*	Intervention Or Exposure Defined Using Valid/reliable Measures	Outcomes Assessed Using Calid/reliable Measures And Implemented Consistently	Confounding Variables Assessed Using Valid/reliable Measures Across All Participants	Outcomes Prespecified And Reported*	Overall Risk Of Bias
Suo et al. 2012 [1598]	Seizure frequency	High	High	SC	High	High	Low	Low	High	SC	High
Suo et al. 2012 [1598]	Seizure freedom	High	High	SC	High	High	Low	Low	High	SC	High

Pre/Post	Outcome	Study Addressed Ootential Confounding†	Study Ruled Out Any Impact From Concurrent Intervention or exposure	Fidelity To Intervention Protocol	Bias Due To Attrition	Outcome Assessor Blinding*	Intervention Or Exposure Defined Using Valid/reliable Measures	Outcomes Assessed Using Calid/reliable Measures And Implemented Consistently	Confounding Variables Assessed Using Valid/reliable Measures Across All Participants	Outcomes Prespecified And Reported*	Overall Risk Of Bias
Wu et al. 2015[1599]	Seizure frequency	High	SC	SC	Low	High	Low	Low	Low	Low	High
Wu et al. 2015[1599]	Seizure freedom	High	SC	SC	Low	High	Low	Low	Low	Low	High
Dressler et al. 2015[355]	Seizure frequency	High	High	SC	SC	High	Low	High	High	SC	High
Dressler et al. 2015[355]	Seizure freedom	High	High	SC	SC	High	Low	High	High	SC	High
Dressler et al. 2015[355]	Adverse events	High	High	SC	SC	High	Low	High	High	SC	High
Kang et al. 2005[1601]	Seizure frequency	High	High	SC	High	High	Low	Low	SC	SC	High
Kang et al. 2005[1601]	Seizure freedom	High	High	SC	High	High	Low	Low	SC	SC	High
Kim et al. 2019[1600]	Seizure frequency	High	High	Low	Low	High	Low	High	High	High	High
Kim et al. 2019[1600]	Adverse events	High	High	Low	Low	High	Low	High	High	High	High
Liu et al. 2021[1602]	Seizure frequency	High	High	SC	Low	High	Low	Low	SC	SC	High

Pre/Post	Outcome	Study Addressed Ootential Confounding†	Study Ruled Out Any Impact From Concurrent Intervention or exposure	Fidelity To Intervention Protocol	Bias Due To Attrition	Outcome Assessor Blinding*	Intervention Or Exposure Defined Using Valid/reliable Measures	Outcomes Assessed Using Calid/reliable Measures And Implemented Consistently	Confounding Variables Assessed Using Valid/reliable Measures Across All Participants	Outcomes Prespecified And Reported*	Overall Risk Of Bias
Liu et al. 2021[1602]	Adverse events	High	High	SC	Low	High	Low	Low	SC	SC	High

We rated risk of bias only for studies for which we rated the strength of evidence (SOE). Other studies are discussed in the text.
Risk of bias items for Pre/Post studies
† Studies were required to report baseline seizure frequency and number of prior antiseizure medications (ASMs)
1 Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
2 Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
3 Did the study maintain fidelity to the intervention protocol?
4 If attrition (overall or differential nonresponse, dropout, loss to followup, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-breat analysis and imputation)?
5 Were the outcome assessors blinded to the intervention or exposure status of participants?
6 Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?
7 Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?
8 Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?
9 Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?
SC: Some concern.

Surgical Interventions

Table C-15. Surgical interventions: Study characteristics

Study	Study Design	Country	Interventions	n	Comparator	n	Study Duration	Funding	Comments
Otsuki et al. 2013[577]	Pre/Post	Japan	Hemispherotomy	18	NA	NA	NR	Health Labor Sciences Research Grant from the Ministry of Health Labor and Welfare of Japan	None

Study	Study Design	Country	Interventions	n	Comparator	n	Study Duration	Funding	Comments
Reinholdson et al. 2015[1605]	Pre/Post	Sweden	Temporal lobe resection (n=12) Frontal lobe resection (n=12) Hemispherotomy (n=12)	36	NA	NA	2 years	Grants from the Swedish Research Council (grant 521-2011-169) and the Sahlgrenska Academy at the University of Gothenburg through the LUA/ALF agreement (grant ALFGBG137431), the Margarethahem Foundation and the Gothenburg Foundation for Neurological Research	None
Kadish et al. 2019[1160]	Pre/Post	Germany	Intralobar resection (n=18) Multilobar resection (n=8) Hemispherotomy (n=22)	48	NA	NA	1 to 14.3 yr (mean 5.2, SD 3.6) for all	NR	None
Steinbok et al. 2009[1606]	Pre/Post	Canada	Hemispheric surgeries (n=48) (including anatomic hemispherectomy, hemidecortication, functional hemispherotomies, periinsular hemispherotomies) Lesionectomies ± cortical resections (n=32) Cortical resection (n=26)	106	NA	NA	1-year post-op or longer for all	No external funding	Seizure outcomes reported from 106 final seizure surgeries (see Table 3)
Loddenkemper et al. 2007[483]	Pre/Post	US	Hemispherectomy (n=14) Focal resection (n=10)	24	NA	NA	Median 6 months (range 4 to 42 months)	NR	None

Study	Study Design	Country	Interventions	n	Comparator	n	Study Duration	Funding	Comments
Sugimoto et al. 1999[1607]	Pre/Post	Canada	Focal cortical resection	10	NA	NA	Mean 38.9 months (range 3 to 86 months)	NR	None
Dunkley et al. 2010[1608]	Pre/Post	United Kingdom	Hemispherotomy (n=27) Multilobar/lobar/focal resection (n=15)	42	NA	NA	Median 5 years, 3 months post-op (range 27 to 158 months)	NR	None
Kumar et al. 2015[1609]	Pre/Post	US	Hemispherotomy	16	NA	NA	Mean 56 months (range 3 to 133 months)	NR	None
Iwasaki et al. 2015[1610]	Pre/Post	Japan	Hemispherotomy	10	NA	NA	Mean 4.2 years (1.5 to 11)	Grant-in-Aid for Scientific Research (No. 25462240) from the Japan Society for the Promotion of Science.	None
Kalbhenn et al. 2019[1611]	Pre/Post	Germany	Posterior disconnection surgery	10	NA	NA	24 months	NR	None
Schramm et al. 2012[1612]	Pre/Post	Germany	Hemispherotomy	21	NA	NA	>1 year post-op	Patient followup: Grants from the Deutsche Forschungsgemeinschaft (DFG) partly within the transregional collaborative research consortium SFB400 “Molecular basis of CNS disorders” and SFB TR3 “Mesio-temporal lobe epilepsies.”	None
Gaggero et al. 2009[1613]	Pre/Post	Italy	Resection	20	NA	NA	1, 4, and 8 years	NR	None
Pinto et al. 2014[1614]	Pre/Post	US	Hemispherectomy /hemispherotomy	15	NA	NA	>1 year	NR	None
Maton et al. 2007[1615]	Pre/Post	US	Resection (temporal lobe)	13	NA	NA	6.3 years (range 1 to 23)	NR	None

Study	Study Design	Country	Interventions	n	Comparator	n	Study Duration	Funding	Comments
Cook et al. 2004[293]	Pre/Post	US	Hemispherectomy/ hemispherotomy	55	NA	NA	6 months, 1 year, 2 years	NR	None
Jonas et al. 2004[294]	Pre/Post	US	Hemispherectomy	16	NA	NA	6 months, 1 year, 2 years, 5 years	NIH grants R01 NS38992 and P05 NS02808 to G.W.M., and R01 NS39505 to R.F.A.	None
Lettori et al. 2007[128]	Pre/Post	Italy	Hemispherectomy	10	NA	NA	6 months, 1 year	NR	None
Roth et al. 2021[1616]	Pre/Post	Multinational	Resective or disconnective surgery (focal resection, lobar / multilobar resection or disconnection, corpus callosotomy, or hemispheric surgery.	64	NA	NA	Median followup 41 months (19 to 104 interquartile range)	NR	Operations performed between 1999 and 2020; excluded infants with hypoxic ischemic encephalopathy; 64 patients undergoing 67 procedures

NA = not applicable; NR = not reported; NIH = National Institute of Health

Table C-16. Surgical interventions: Patient characteristics

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Otsuki et al. 2013[577]	Consecutive children who had medically refractory epilepsy with cortical dysplasia and undewent epilepsy surgery at less than 6 years of age at the National Center of Neurology and Psychiatry from December 2000 to August 2011. Patients with tuberous sclerosis, dysplastic tumors, and encephalomalacia were excluded from the study.	Hemispherotomy	18	NR	15 patients (age 0); 1 patients (age 2) 2 patients (age 3)	All patients had drug-resistant multiple daily seizures, such as epileptic spasm, tonic seizures, or epilepsia partialis continua.	NR	None
Reinholdson et al. 2015[1605]	Swedish National Epilepsy Surgery Register data capturing population based, observational cohort of children under 4 years of age undergoing resective epilepsy surgery in Sweden between 1995 and 2010	Temporal lobe resection (n=12) Frontal lobe resection (n=12) Hemispherotomy (n=12)	36	NR for subgroup)	NR for subgroup 2 years 1 month (mean and median), range 2 months to 4 years for overall study	NR	ASM currently used: 2.2 (Mean), 2 (Median), Range 0 to 4) ASM previously tried: 1.8 (mean), 1 (median), range (0 to 9)	None

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Kadish et al. 2019[1160]	Consecutive patients, selected from an institutional database, that 1) underwent presurgical evaluation in the cooperating Epilepsy Surgery Centers Freiburg, Heidelberg, Kork and Kiel according to the same protocol, 2) had epilepsy surgery before the age of 3 in 2001-2014 in the Epilepsy Center Freiburg, 3) were followed up >1 year after surgery	Hemispherotomy (n=22) Intralobar resection (n=18) Multilobar resection (n=8)	48	24 male	1.1 ± 0.7 year	NR	At time of surgery: mean 2 ASM 9 (median 5) ASM before first surgery: 27% additionally received steroids and 8% ketogenic diet	Patient numbers reported here represent first surgeries reported by the study.
Steinbok et al. 2009[1606]	Patients age < 3 undergoing epilepsy surgery at multiple centers across Canada from January 1987 to September 2005. Patients with surgery for a lesion, such as a tumor, who happened to present with seizures, but for whom the surgery was done for the lesion rather than the epilepsy were excluded.	Hemispheric surgeries (n=48) (including anatomic hemispherectomy, hemidecortication, functional hemispherotomies, periinsular hemispherotomies) Lesionectomies ± cortical resections (n=32) Cortical resection (n=26)	106	NR	NR for subgroup of interest (final seizure surgery)	NR for subgroup of interest (final seizure surgery)	NR	The study presents data on 116 patients undergoing 151 surgical procedures; however, seizure outcomes are reported by 106 final seizure surgeries only. Age at surgery for overall population (n=116) was mean 15.8 months (range 1–35 months)

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Loddenkemper et al. 2007[483]	50 infants <3 years old among 251 consecutive pediatric patients (<18 years old) undergoing epilepsy surgery at our center between 1989 and 2001 were considered for inclusion	Hemispherectomy (n=14) Focal resection (n=10)	24	18 male	Age of surgery: median 14 months (range: 3–34 months)	Seizure etiology: Patient undergoing hemispherectomy (7 HME, 5 MCD, 2 SWS) Patients undergoing focal resection (7 MCD, 2 MCD and ganglioma, 1 TS) Patients presented with a median of 2 different semiological seizure types (range: 1– 4). Seizure semiology included tonic seizures (15), clonic seizures (15), epileptic spasm (11), eye versive seizures (7), hypomotor seizures (5), and myoclonic seizures (3)	At surgery, patients were taking a median of 3 ASM (range: 0 –5)	None

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Sugimoto et al. 1999[1607]	Children, aged 0-3 years, who had epilepsy surgery at the Hospital for Sick Children, Toronto, Canada, from 1991 to 1996	Focal cortical resection	10	4 male	Age of surgery: mean 18.5 months (range 8 to 34)	Seizure type at onset: Partial motor onset (unilateral) : 3 Partial motor onset: bilateral: 1 Partial motor onset, secondary generalization: 3 Complex partial seizures: 1 Partial motor seizures, changing to generalized tonic clonic seizures: 1 Partial motor seizures, changing to complex partial seizures: 1	NR	None
Kumar et al. 2015[1609]	All children under the age of 1 year undergoing surgical intervention to treat medically refractory epilepsy at Children's Hospital of Colorado between 2002 and 2013	Hemispherotomy	16	NR (by procedure)	4.5 months (Rnage 0.25 to 11.5)	5 focal, 4 spasm, 4 imxed, 2 tonic clonic, 1 no clinical correlate	NR	None
Iwasaki et al. 2015[1610]	Consecutive patients underwent hemispherotomy for treatment of intractable epilepsy at Tohoku University between 2001 and 2012	Hemispherotomy	10	7 male, 4 female	Mean 9 months (range 3 to 24)	NR		None

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Kalbhenn et al. 2019[1611]	29 consecutive patients undergoing posterior disconnection surgery between 2005 and 2017 for the treatment of refractory posterior quadrantic epilepsy at a single center	Posterior disconnection surgery	10	NR	Mean 1.65 years (range 0.6 to 2.6)	6 Type B, 4 Type C	NR	None
Schramm et al. 2012[1612]	All patients up to the age of 18 undergoing hemispherotomy at the Bonn University Medical Center operated on between 1990 and the end of 2009 with a minimum followup of 1 year.	Hemispherotomy	21	NR	Age <3	NR	NR	None
Gaggero et al. 2009[1613]	Patients age <3 with primary supratentorial hemispheric brain tumors receiving care at ‘‘G. Gaslini’’ Children’s Hospital, Genoa, Italy, during a 10-year period	Resection	20	12 male, 8 female	< 36 months	Focal: 12 Generalized: 8 Convulsive status epilepticus: 5	One ASM: 9 2 ASM: 7 3 ASM: 4. The most commonly administered drugs were valproate in 14 (70%), levetiracetam in 8 (40%) carbamazepine in 6 (30%), phenytoin and phenobarbital in 4 (20%)	None

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Pinto et al. 2014[1614]	Children undergoing epilepsy surgery (anatomic hemispherectomy, functional hemispherectomy, and peri-insular hemispherotomy) at Children's Hospital Boston from 1997 to 2011	Anatomic hemispherectomy (n=10) Functional hemispherectomy (n=4) Periinsular hemispherectomy (n=1)	15	NR	Mean 12.2 months (range 5 to 24)	6 focal seizures (tonic, tonic clonic or complex partial), 2 generalized tonic clonic and focal seizures, 6 infantile spasm and focal seizures, 1 infantile spasm and generalized tonic clonic seizures	NR	None
Maton et al. 2007[1615]	Patients age <5 undergoing temporal lobe resection at Miami Children's Hospital between 1979 and 2003.	Resection (temporal lobe)	13	10 male, 3 female (6 with developmental delay)	14.8 months (SD 8.1), range 6 to 33	5 SpASM with or without partial seizure, 4 psychomotor seizures followed by prominent motor changes, 2 psychomotor seizures without motor changes, 2 pure motor seizures	NR	None
Cook et al. 2004[293]	Children with intractable seizures undergoing hemispherectomy at UCLA's Pediatric Epilepsy Surgery Program between 1986 and 2002	Hemispherectomy/ hemispherotomy	55	NR	Mean 2.5 (SD 0.4)	53% of patients with cortical dysplasia had a history of infantile spasm; no other information provided	NR	None
Jonas et al. 2004[294]	Cerebral hemispherectomy patients operated at UCLA's Pediatric Epilepsy Surgery Program from 1986 to 2002 (subset of patients included in[293])	Hemispherectomy	16	9 male, 7 female	1.5 years (SD 1.2)	9 of 16 with infantile spasm	2.5 +-0.9 ASM	None

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Lettori et al. 2007[128]	Patients treated with hemispherectomy within 5 years of age in the Child Neurosurgery Unit of Catholic University, Rome from 1980 to December 2003, we enrolled in the study only 19 thoroughly studied children, drug resistant with at least 3 drugs at maximal dosage with no seizure control	Hemispherectomy	10	6 male, 4 female	Mean 11.3 months (range 5 to 20)	2 partial seizures only; 3 partial with partial status epilepticus ± myclonic, and tonic spasm; 3 spasm, partial seizures with or without partial status epilepticus; 1 spasm and partial, 1 tonic, partial, myoclonias	NR	None

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Roth et al. 2021[1616]	All children undergoing epilepsy surgery at <3 months or 100 days beyond 40 weeks gestation. For inclusion, infants were required to have ≥ 6 months of followup, unless the patient died. Excluded infants with epilepsy due to hypoxic ischemic encephalopathy.	64 children, 67 surgeries Focal resections (7 lobectomies, 12 lesionectomy) Hemispheric surgeries: 48 (25 peri-insular, 12 vertical functional hemispherectomies, 10 anatomic hemispherectomies, 1 unknown)	64	30 female, 34 male	Focal surgery: 62 days (interquartile range 43 to 86) Hemispheric surgery: 78 (interquartile range 68 to 94)	Seizure type available for 63 patients: 33 focal seizures, 6 generalized, 24 focal and generalized 28 cortical dysplasia, 17 hemimegalencephaly, 5 tubers, 4 nonspecific findings, 1 glioneuronal hamartoma, 1 stroke, 1 Sturge Weber, 1 hematoma 6 unknown	Median 4 (Interquartile range 3 to 4), range 1 to 11 ASMs prior to surgery. Continuous intravenous barbiturates or benzodiazepines (n=41) Intubated before surgery (n=22)	Seizure age of onset 0 to 49 days (6.6 ±11.8). 4 had suspected seizures prior to birth. 27 (42%) had experienced status epilepticus Hemispheric (including hemispherotomy, disconnection surgery) Hemi-spherectomy (such as anatomic hemi-spherectomy, regardless of surgical technique-including combined resective/disconnective surgery) or focal (including lobar or multilobar resections_

NA: not applicable; NR: not reported; NRFS: not reported for the subgroup; IQR: interquartile range; ASM: antiseizure medications

Table C-17. Surgical interventions: Hemispherectomy/hemispherotomy seizure outcomes

Study	Intervention	n	Baseline Number of Seizures	Seizure Outcomes	Comments
Cook et al. 2004[293] Jonas et al. 2004[294]	Anatomic hemispherectomy (n=14) Functional hemispherectomy (n=15) Hemispherotomy (n=26)	55 infants with cortical dysplasia (Subgroup of 16 infants with HME reported in Jonas[294])	NR	**Seizure Freedom**: 6 months after surgery • Overall: 44 of 55 (80%) seizure free • Anatomic hemispherectomy: 12 of 14 (86%) • Functional hemispherectomy/Hemispherotomy: 32 of 41 (78%) **Seizure Freedom**: 1 year after surgery • Overall: 41 of 55 (75%) seizure free • Anatomic hemispherectomy: 12 of 14 (86%) • Functional hemispherectomy/Hemispherotomy: 29 of 41 (71%) **Seizure Freedom**: 2 years after surgery • Overall: 42 (76%) seizure free • Anatomic hemispherectomy: 12 of 14 (86%) • Functional hemispherectomy/Hemispherotomy: 30 of 41 (73%) *Subgroup of 16 infants with HME*: • Seizure free at 6 months: 15 • Seizure free at 1 year: 14 • Seizure free at 2 years: 13 • Seizure free at 5 years: 6	None
Iwasaki et al. 2015[1610]	Hemispherotomy (3 periinsular hemispherotomies, 7 vertical hemispherotomies)	10	NR	**Engel Outcome:** (mean 4.2 years after surgery, (range 1.5 to 11) Engel I: 8 Engel II: 0 Engel III: 3 Engel IV: 0 **Favorable Outcome (Engel I or II): 8 of 10 (80%)**	None

Study	Intervention	n	Baseline Number of Seizures	Seizure Outcomes	Comments
Kadish et al. 2019[1160]	Hemispherotomy (n=22) Intralobar resection (n=18) Multilobar resection (n=8)	48	NR	**Engel I (after first surgery, timepoint not provided, from Figure 1)**: • Hemispherotomy: 12 of 22 (54.5%) • Intralobar resection: 13 of 18 (72.2%) • Multilobar resection: 3 of 8 (37.5%) Needed Second Surgery: • Hemispherotomy: 0 • Intralobar resection: 2 • Multilobar resection: 2 **Engel Score**: mean 5.2 years, SD 3.6 after surgery, range 1 to 14.3 years (this outcome was reported by final surgery, Table 1) • Intralobar: Engel I: 13, Engel II-IV: 4 • Hemispherotomy or Multilobar resection: Engel I: 19, Engel II-IV: 15	Engel I outcomes were extracted from first surgeries reported by study authors, study Figure 1.
Kumar et al. 2015[1609]	Hemispherotomy	16	48 (3 to 200) per day	**Engel Outcome**: (mean 56 months, range 3 to 133) • Engel I: 13 • Engel II: 1 • Engel III: 0 • Engel IV: 2 **Favorable Outcome (Engel I or II): 14 of 16 (88%)**	None

Study	Intervention	n	Baseline Number of Seizures	Seizure Outcomes	Comments
Lettori et al. 2007[128]	Hemispherectomy (6 anatomic, 2 functional, 1 functional + hemidecortication, 1 hemidecortication)	10	NR	**Engel Outcome**: (6 months) • Engel Ia: 7 • Engel Ib: 1 • Engel IIb: 2 **Seizure Freedom**: 70% (7 of 10) **Favorable Outcome (Engel I or II):** 10 of 10 (100%) **Engel Outcome:** (1 year) • Engel Ia: 5 • **Engel Ib: 3** • Engel IIa: 1 • **Engel IIIa: 1** **Seizure Freedom:** 50% (5 of 10) **Favorable Outcome (Engel I or II**): 9 of 10 (90%)	None
Loddenkemper et al. 2007[483]	Hemispherectomy (n=14) Focal resections (n=10)	24	Hemispherctomy: 26 seizures/day Focal resection: 27 seizures/day	At median 6 months (4 to 42 months) after surgery: **Seizure Freedom**: • Hemispherectomy: 9 of 14 (64%) became seizure free • Focal resection: 7 of 10 (70%) became seizure free **Seizure Frequency (seizures per day)**: • Hemispherectomy: 26.2 (before) to 1.6 (after surgery) • Focal resection: 27.4 (before) to 0.9 (after surgery) **Favorable outcome (>50% reduction after surgery)**: • Hemispherectomy: 13 of 14 • Focal resection: 10 of 10 **ASM use**: • Hemispherectomy: 2.9 (before) to 1.6 (after) • Focal resection: 3 (before) to 1.3 (after)	Infant undergoing hemispherectomy and not achieving 50% reduction was Case 23, an infant with HME who underwent hemispherectomy. Surgeries (13 right, 11 left) included 14 hemispherectomies and 10 focal resections (3 frontal, 3 frontoparietal, 2 parietal, 1 parieto-occipital, and 1 occipital).

Study	Intervention	n	Baseline Number of Seizures	Seizure Outcomes	Comments
Otsuki et al. 2013[577]	Hemispherotomy	18 infants with cortical dysplasia	NR	Followup interval for hemispherotomy NR; however, overall followup for all study patients was mean 4 years, 4 months (1 to 11 years) **ILAE Class**: • ILAE class I (seizure free): 12 of 18 (66.6%) • ILAE class IV: 1 • ILAE class V: 5 **Favorable outcome (ILAE I to IV):** 13 of 18 (72%)	Figure 2 confirms that subgroup of infants underoing hemispheric surgery met age criteria for inclusion. Data for efficacy are drawn from Figure 7 of the article.
Pinto et al. 2014[1614]	Anatomic hemispherectomy (n=10) Functional hemispherectomy (n=4) Periinsular hemispherectomy (n=1)	15	NR by subgroup	**Engel Outcomes**: (at least 1 year after surgery) **Anatomic Hemispherectomy**: (n=10) • Engel Ia: 1 • Engel I: 7 • Engel II: 0 • Engel III or IIIa: 2 • Engel IV: 0 **Seizure Freedom:** 1 of 10 **Favorable outcome (Engel I or II)**: 8 of 10 (80%) **Functional Hemispherectomy/Periinsular Hemispherotomy**: (n=5) • Engel I: 2 • Engel II: 0 • Engel III: 2 • Engel IV: 1 **Seizure Freedom:** 0 **Favorable outcome (Engel I or II)**:2 of 5 (40%)	Anatomic hemispherectomy patients: 6 HME, 1 polymicrogyria, 2 cortical dysplasia, 1 stroke Functional hemispherectomy/ Periinsular hemispherotomy: 2 HME, 2 cortical dysplasia, 1 stroke

Study	Intervention	n	Baseline Number of Seizures	Seizure Outcomes	Comments
Reinholdson et al. 2015[1605]	Hemispherotomy (n=12) Temporal lobe resection (n=12) Frontal lobe resection (n=12)	36	NR	At 2 years after surgery **Seizure Freedom**: • Hemispherotomy: 7 of 12 • Temporal lobe resection: 9 of 12 • Frontal lobe resection: 4 of 12 **Seizure Frequency**: **Hemispherotomy**: • Seizure free: 7 • ≥ 75% reduction: 2 • 50 to 74% reduction: 2 • 0 to 49% reduction: 1 **Favorable Outcome (>50% Reduction)**: 11 of 12 (92%) **Temporal lobe resection**: • Seizure free: 9 • ≥ 75% reduction: 2 • 50 to 74% reduction: 1 • 0 to 49% reduction: 1 **Favorable Outcome (>50% Reduction)**: 12 of 12 (100%) **Frontal lobe resection**: • Seizure free: 4 • ≥ 75% reduction: 2 • 50 to 74% reduction: 3 • 0 to 49% reduction: 0 • Increased frequency: 3 **Favorable Outcome (>50% Reduction)**: 9 of 12 (75%)	None

Study	Intervention	n	Baseline Number of Seizures	Seizure Outcomes	Comments
Roth et al. 2021[1616]	Hemispherectomy/Hemisphereotomy (=48) 25 periinsular 12 vertical functional hemisphereotomy 10 anatomic hemispherectomy 1 unkown Focal resection (n=17)	48	NR	At median followup: 51 months (interquartile range 27 to 126) **ILAE Outcome**: ILAE I: 30 (70%) ILAE II: 1 (2%) ILAE III: 3 (7%) ILAE IV: 3 (7%) ILAE V: 6 (14%) **Favorable outcome (ILAE I to IV):** 37 of 43 (86%)	Etiologies were NR separately for hemispheric surgery patients. As per author correspondence, Table 3 includes 43 infants undergoing hemispheric surgery.
Schramm et al. 2012[1612]	Hemispherotomy	21	NR	At ≥ 1 year after surgery: **ILAE I**: 16 of 21 (76%)	None

Study	Intervention	n	Baseline Number of Seizures	Seizure Outcomes	Comments
Steinbok et al. 2009[1606]	Hemispheric (n=48) Lesionectomy (n=32) Cortical resection (n=26)	106	NR	At 1 year after surgery or longer: **Engel Outcome**: **Hemispheric:** • Engel I: 28 • Engel II: 7 • Engel III: 8 • Engel IV: 5 **Favorable Outcome (Engel I or II)**: 35 of 48 (73%) **Lesionectomy:** • Engel I: 29 • Engel II: 1 • Engel III:1 • Engel IV:1 **Favorable Outcome (Engel I or II):** 30 of 32 (94%) **Cortical Resection**: • Engel I: 15 • Engel II: 7 • Engel III: 3 • Engel IV: 1 **Favorable Outcome (Engel I or II):** 22 of 26 (85%)	These represent the final seizure surgery for 116 children.

HME – Hemimegalencephaly; ILAE – International League Against Epilepsy; NR – Not reported

Table C-18. Surgical interventions: Other resection seizure outcomes

Study	Intervention	n	Baseline Number of Seizures	Seizure Outcomes	Comments
Kadish et al. 2019[1160]	Hemispherotomy (n=22) Intralobar resection (n=18) Multilobar resection (n=8)	48	NR	**Engel I (after first surgery, timepoint not provided, from Figure 1)**: • Hemispherotomy: 12 of 22 (54.5%) • Intralobar resection: 13 of 18 (72.2%) • Multilobar resection: 3 of 8 (37.5%) Needed Second Surgery: • Hemispherotomy: 0 • Intralobar resection: 2 • Multilobar resection: 2 **Engel Score**: mean 5.2 years, SD 3.6 after surgery, range 1 to 14.3 years (this outcome was reported by final surgery, Table 1) • Intralobar: Engel I: 13, Engel II-IV: 4 • Hemispherotomy or Multilobar resection: Engel I: 19, Engel II-IV: 15	Engel I outcomes were extracted from first surgeries reported by study authors, study Figure 1.
Kalbhenn et al. 2019[1611]	Posterior disconnection surgery	10	NR	At followup 24 months after surgery **Seizure freedom**: 5 of 10 (50%)	6 focal cortical dysplasia, 2 ganglioma + FCD, 1 polymicrogyria, 1 meningeal angiomatosis

Study	Intervention	n	Baseline Number of Seizures	Seizure Outcomes	Comments
Loddenkemper et al. 2007[483]	Hemispherectomy (n=14) Focal resections (n=10)	24	Hemispherctomy: 26 seizures/day Focal resection: 27 seizures/day	At median 6 months (4 to 42 months) after surgery: **Seizure Freedom**: • Hemispherectomy: 9 of 14 (64%) became seizure free • Focal resection: 7 of 10 (70%) became seizure free **Seizure Frequency (seizures per day)**: • Hemispherectomy: 26.2 (before) to 1.6 (after surgery) • Focal resection: 27.4 (before) to 0.9 (after surgery) **Favorable outcome (>50% reduction after surgery)**: • Hemispherectomy: 13 of 14 • Focal resection: 10 of 10 **ASM use**: • Hemispherectomy: 2.9 (before) to 1.6 (after) Focal resection: 3 (before) to 1.3 (after)	Infant undergoing hemispherectomy and not achieving 50% reduction was Case 23, an infant with HME who underwent hemispherectomy. Surgeries (13 right, 11 left) included 14 hemispherectomies and 10 focal resections (3 frontal, 3 frontoparietal, 2 parietal, 1 parieto-occipital, and 1 occipital).
Maton et al. 2007[1615]	Temporal lobe resection	13	Daily seizures (n=11), Weekly seizures (n=2)	**Engel Outcome**: At mean 6.3 years (range 1 to 23) after surgery Engel I: 9 Engel II: 2 Engel: IV: 2 **Favorable outcome (Engel I or II):** 11 of 13 (85%)	Cortical dysplasia: 4 Gliosis: 2 Ganglioma: 2 Astrocytoma: 2 Glioma: 1 HIE: 1 Gliomatosis cerebrii: 1

Study	Intervention	n	Baseline Number of Seizures	Seizure Outcomes	Comments
Reinholdson et al. 2015[1605]	Hemispherotomy (n=12) Temporal lobe resection (n=12) Frontal lobe resection (n=12)	36	NR	At 2 years after surgery **Seizure Freedom**: • Hemispherotomy: 7 of 12 • Temporal lobe resection: 8 of 12 • Frontal lobe resection: 4 of 12 **Seizure Frequency**: **Hemispherotomy**: • Seizure Free: 7 • ≥ 75% reduction: 2 • 50 to 74% reduction: 2 • 0 to 49% reduction: 1 **Favorable outcome (>50% reduction**): 11 of 12 **Temporal lobe resection**: • Seizure Free: 8 • ≥ 75% reduction: 2 • 50 to 74% reduction: 1 • 0 to 49% reduction: 1 **Favorable outcome (>50% reduction)**: 11 of 12 **Frontal lobe resection**: • Seizure free: 4 • ≥ 75% reduction: 2 • 50 to 74% reduction: 3 • 0 to 49% reduction: 0 • Increased frequency: 3 **Favorable outcome (>50% reduction)**: 9 of 12	None

Study	Intervention	n	Baseline Number of Seizures	Seizure Outcomes	Comments
Roth et al. 2021[1616]	Hemispherectomy/Hemispherotomy (n=48) Focal resection (n=19)	19	NR	At median followup: 24 months (interquartile range 5 to 55) **ILAE Outcome**: ILAE I: 9 (56%) ILAE II: 0 (0%) ILAE III: 2 (12%) ILAE IV: 4 (25%) ILAE V: 1 (6%) **Favorable outcome (ILAE I to IV)**: 15 of 16 (94%)	Baseline number of seizures and seizure etiology NR separately for patients undergoing focal resection. As per author correspondence, Table 3 includes 16 infants undergoing hemispheric surgery.

Study	Intervention	n	Baseline Number of Seizures	Seizure Outcomes	Comments
Steinbok et al. 2009[1606]	Hemispheric (n=48) Lesionectomy (n=32) Cortical resection (n=26)	106	NR	At 1 year after surgery or longer: **Engel Outcome**: **Hemispheric:** Engel I: 28 Engel II: 7 Engel III: 8 Engel IV: 5 **Favorable outcome (Engel I or II)**: 35 of 48 **Lesionectomy:** Engel I: 29 Engel II: 1 Engel III:1 Engel IV:1 **Favorable outcome (Engel I or II)**: 30 of 32 **Cortical Resection**: Engel I: 15 Engel II: 7 Engel III: 3 Engel IV: 1 **Favorable outcome (Engel I or II)**: 22 of 26	None
Sugimoto et al. 1999[1607]	Focal cortical resection	10	NR	At followup mean 38.9 months (range 3 to 80) after surgery (3.2 y, range 0.25 to 6.7) **Seizure Freedom (Engel Ia):** 4 of 10 (40%) **Engel Outcome**: Engel I-A: 4 Engel II-A: 1 Engel III-A: 3 Engel IV-A: 1 Engel IV-B: 1 **Favorable Outcome (Engel I or II)**: 5 of 10 (50%)	None

FCD- Focal cortical dysplasia; HIE= Hypoxic ischemic encephalopathy; NA = not applicable; NR = not reported

Table C-19. Surgical interventions: Supratentorial tumor resection seizure outcomes

Study	Intervention	n	Baseline	Seizure Outcomes	Comments
Gaggero et al. 2009[1613]	Resection of supratentorial tumors	20	NR	1 year: (n=20) • Engel I: 9 • Engel II: 7 • Engel III: 2 • Engel IV: 2 80% (16 of 20) Engel I or II 4 years: (n=20) • Engel I: 11 • Engel II: 5 • Engel III: 2 • Engel IV: 2 80% (16 of 20) Engel I or II 8 years: (n=17, 3 patients died from tumor recurrence) • Engel I: 9 • Engel II: 4 • Engel III: 2 • Engel IV: 2 76% (13 of 17) Engel I or II	The extent of resection was total in 14 (70%) patients (7 with extratemporal lesions) and subtotal in all 6 with extratemporal lesions. No intraoperative deaths occurred. A second or a third operation was required in 2 subjects.

Table C-20. Surgical interventions: Other effectiveness outcomes

Study	Intervention	Age at Surgery	Functional Outcomes	Comments
Loddenkemper et al. 2007[483]	Hemispherectomy (n=14) Focal resection (n=10)	Median 14 months (3 to 34 months)	**Preoperative Assessment (median 12 months, range 3 to 34)** • Median Developmental age: Bayley scale 3 months (mean 5.83 months). • Developmental Quotient (DQ) (DQ): Median: 37 (range 0-92) • Developmental delays: 22 infants **Postoperative Assessment (performed at median 24 months) (10 to 53 months) or median 6 months (range 4 to 42 months) after surgery** • Median Developmental age: Bayley scale, 9 months (mean 11.94 months). • DQ: Median: 49 (range 2-92) • Developmental delays: 18 infants (not significantly changed compared to pre-op, p=0.125 McNemar) • Improved DQ: Surgery at <1 year 10 of 11, Surgery at >1 year 6 of 13. Younger age at surgery was correlated with improvement in DQ (correlation coefficient 0.72, p<0.001)	Study notes of 50 consecutive infants considered for inclusion 26/50 (52%) were not included due to incomplete data or use of other neuropsychological tests. Median developmental age was assessed using the Bayley scale. DQ: ratio of Bayley mental age divided by subject's biological age x 100).

Study	Intervention	Age at Surgery	Functional Outcomes	Comments
Jonas et al. 2004[294]	Hemispherectomy	1.5 years ± 1.2	**Vineland DQ:** Compared to before surgery, the Vineland Developmental Quotient • 6 to 24 months difference: 9.1 (SD=16) **Spoken language rank (SLR)**: The SLR increased from 0.33±0.5 (preoperative) to 1.4±1.8 (after surgery)	Mean age at postsurgery language sampling: 7.3 ± 4 years "For children who too young to be expected to speak no presurgery language data were collected. For children who did not yet speak or were speaking primarily in one- to two-word utterances language was assessed by means of the MacArthur Communicative Development Inventories (MCDI). For children who consistently produced two-word or longer utterances, language samples were collected by means of an interview with an examiner. These language samples were audio tape recorded, transcribed, and analyzed for grammatic and lexical content, and each language sample or MCDI assigned a Spoken Language Rank (SLR) as previously published using the following six-point scale: SLR 0, no language; SLR 1, fewer than 20 words; SLR 2, more than 20 words but no word combinations; SLR 3, short telegraphic utterances typical of the root infinitive (RI) stage in normal language development; SLR 4, beyond the RI (root infinitive/telegraphic) stage with only occasional errors in the use of functional category elements but no complementizer phrase (CP) embeddings (e.g., relative clauses and other clausal embeddings); SLR 5, fluent speech plus CP embeddings (but not the full complement of error free structures in the mature grammar); and SLR 6, mature grammar."

Study	Intervention	Age at Surgery	Functional Outcomes	Comments
Lettori et al. 2007[128]	Hemispherectomy	Mean 11.3 months (5 to 20)	**Preoperative:** Functional status: • Unable to assess at baseline: 8 • Dependent: 2 **Postoperative: (7.7 years, 2.1 to 11.2)** Functional status: • Dependent: 6 • Semi-independent: 3 • Independent: 1 Although DQ/IQ was measured, NR for subgroup of interest	**Cognitve Assessment**: Different scales as appropriate for the child's chronological age and level of functioning: Griffiths' Mental Development Scales or Uzgiris-Hunt Scales in children below four years, Wechsler Preschool and Primary Scale of Intelligence (WIPPSI) between 4 and 6 years, and Wechsler Intelligence Scale for Children-Revised (WISC-R) above six years. We considered a Developmental Quotient (DQ) or Intellective Quotient (QI) higher than 85 as normal, borderline between 70 and 85, mildly impaired between 50 and 70, moderately between 35 and 50, and severely when lower than 35. **Functional Status:** Determined by observation of patients and interviews with parents, and was defined in three categories: (a) dependent,when full assistance was required including living functions (eating, dressing, etc), (b) semi-independent, when almost-adequate daily living functions were present, even though there were needs of special education programs and cares, and (c) independent, when children fully coped physical disabilities.
Sugimoto et al. 1999[1607]	Focal cortical resection	NR	**Delays:** Pre-op: • 8 of 10 with delay Post-op: • Improved: 4 of 9 • Good: 2 of 9 • Severe delay: 1 of 9	No details provided on how delay was measured.

NA = not applicable; NR = not reported; NRFS = not reported for the subgroup

Table C-21. Risk of bias for pre/post studies: Hemispherectomy/hemispherotomy

Study	Specific Outcome measure	Study Addressed Ootential Confounding†	Study Ruled Out Any Impact From Concurrent Intervention or exposure***	Fidelity To Intervention Protocol	Bias Due To Attrition	Outcome Assessor Blinding*	Intervention Or Exposure Defined Using Valid/reliable Measures**	Outcomes Assessed Using Calid/reliable Measures And Implemented Consistently	Confounding Variables Assessed Using Valid/reliable Measures Across All Participants	Outcomes Prespecified And Reported*	Overall Risk Of Bias
Cook et al.[293]	Seizure freedom	High	Low	Low	Low	Low	Low	Low	SC	Low	High
Lettori et al.[128]	Seizure freedom	Low	Low	Low	Low	High	Low	High	Low	High	High
Loddenkemper et al.[483]	Seizure freedom	Low	Low	Low	High	Low	Low	Low	Low	Low	High
Otsuki et al.[577]	Seizure freedom	SC	Low	Low	Low	Low	Low	Low	Low	Low	High
Pinto et al.[1614]	Seizure freedom	High	Low	Low	Low	Low	Low	Low	SC	Low	High
Reinholdson et al.[1605]	Seizure freedom	High	Low	Low	Low	Low	Low	Low	High	Low	High
Schramm et al.[1612]	Seizure freedom	SC	Low	Low	Low	Low	Low	Low	SC	Low	High
Roth et al.[1616]	Seizure freedom	High	Low	Low	Low	High	Low	High	High	High	High
Iwasaki et al.[1610]	Seizure frequency	High	Low	Low	Low	High	Low	High	SC	High	High
Kadish et al.[1160]	Seizure frequency	SC	Low	Low	Low	Low	Low	Low	SC	Low	High
Kumar et al.[1609]	Seizure frequency	Low	Low	Low	Low	High	Low	High	SC	High	High
Lettori et al.[128]	Seizure frequency	Low	Low	Low	Low	High	Low	High	Low	High	High
Loddenkempber et al.[483]	Seizure frequency	Low	Low	Low	High	High	Low	High	Low	High	High

Study	Specific Outcome measure	Study Addressed Ootential Confounding†	Study Ruled Out Any Impact From Concurrent Intervention or exposure***	Fidelity To Intervention Protocol	Bias Due To Attrition	Outcome Assessor Blinding*	Intervention Or Exposure Defined Using Valid/reliable Measures**	Outcomes Assessed Using Calid/reliable Measures And Implemented Consistently	Confounding Variables Assessed Using Valid/reliable Measures Across All Participants	Outcomes Prespecified And Reported*	Overall Risk Of Bias
Otsuki et al.[577]	Seizure frequency	SC	Low	Low	Low	High	Low	High	SC	High	High
Pinto et al.[1614]	Seizure frequency	High	Low	Low	Low	High	Low	High	SC	High	High
Reinholdson et al.[1605]	Seizure frequency	High	Low	Low	Low	Low	Low	High	High	High	High
Roth et al.[1616]	Seizure frequency	High	Low	Low	Low	HIgh	Low	High	High	High	High
Steinbok et al.[1606]	Seizure frequency	SC	Low	Low	SC	High	Low	High	SC	High	High

† Factors considered included whether studies reported seizure etiology, baseline seizure rate, or concurrent therapies such as number of antiseizure medications (ASMs) or specific ASM used.

*As all studies used a retrospective pre/post design, no outcome assessors were blinded and no outcomes were prespecified. However, we judged seizure freedom (and mortality) to not be affected by lack of blinding or prespecification of outcomes, so these were rated low risk of bias.

** All studies described the type of surgical procedure, so we rated this low risk of bias for all studies.

*** This domain was rated low as we felt it was unlikely another intervention would be initiated at the same time as surgery.

Overall risk of bias for all studies was rated High, as no studies had a control group.

Table C-22. Risk of bias for pre/post studies: Nonhemispheric procedures (tumor resection, other resections)

Study	Specific Outcome measure	Study Addressed Ootential Confoundingt	Study Ruled Out Any Impact From Concurrent Intervention or exposure***	Fidelity To Intervention Protocol	Bias Due To Attrition	Outcome Assessor Blinding*	Intervention Or Exposure Defined Using Valid/reliable Measures**	Outcomes Assessed Using Calid/reliable Measures And Implemented Consistently	Confounding Variables Assessed Using Valid/reliable Measures Across All Participants	Outcomes Prespecified And Reported*	Overall Risk Of Bias
Kalbhenn et al. 2019[1611] (Posterior disconnection)	Seizure freedom	High	Low	Low	Low	Low	Low	Low	Some concerns	Low	High
Loddenkemper et al. 2007[483] (Focal cortical resection)	Seizure freedom	Low	Low	Low	Low	Low	Low	Low	Low	Low	High
Reinholdson et al. 2015[1605] (Temporal/ frontallLobe resection)	Seizure freedom	High	Low	Low	Low	Low	Low	Low	High	Low	High
Sugimoto et al. 1999[1607] (Focal cortical resection)	Seizure freedom	Some concerns	Low	Low	Low	Low	Low	Low	High	Low	High
Roth et al.[1616]	Seizure freedom	High	Low	Low	Low	High	Low	High	High	High	High
Kadish et al. 2019[1160] (Intralobar resection)	Seizure frequency	Some concerns	Low	Low	Low	High	Low	High	Some concerns	High	High
Loddenkemper et al. 2007[483] (Focal cortical resection)	Seizure frequency	Low	Low	Low	Low	Low	Low	Low	Low	Low	High

Study	Specific Outcome measure	Study Addressed Ootential Confounding†	Study Ruled Out Any Impact From Concurrent Intervention or exposure***	Fidelity To Intervention Protocol	Bias Due To Attrition	Outcome Assessor Blinding*	Intervention Or Exposure Defined Using Valid/reliable Measures**	Outcomes Assessed Using Calid/reliable Measures And Implemented Consistently	Confounding Variables Assessed Using Valid/reliable Measures Across All Participants	Outcomes Prespecified And Reported*	Overall Risk Of Bias
Maton et al. 2007[1615] (Temporal lobe resection)	Seizure frequency	High	Low	Low	Low	High	Low	High	High	High	High
Reinholdson et al. 2015[1605] (Temporal/ frontal Lobe resection)	Seizure frequency	High	Low	Low	Low	High	Low	High	High	Low	High
Roth et al.[1616] (Non-hemispheric)	Seizure frequency	High	Low	Low	Low	HIgh	Low	High	High	High	High
Steinbok et al. 2009[1606] (Lesionectomy/ cortical resection)	Seizure frequency	High	Low	Low	Low	High	Low	High	Some concerns	High	High
Sugimoto et al. 1999[1607] (Focal cortical resection)	Seizure frequency	High	Low	Low	Low	High	Low	High	High	High	High
Gaggero et al.[1613] (Tumor resection)	Seizure frequency	Some concerns	Low	Low	Low	High	Low	High	Some concerns	High	High

† Factors considered included whether studies reported seizure etiology, baseline seizure rate, or concurrent therapies such as number of antiseizure medications (ASM) or specific ASM used.

*As all studies used a retrospective pre/post design, no outcome assessors were blinded and no outcomes were prespecified. However, we judged seizure freedom (and mortality) to not be affected by lack of blinding or prespecification of outcomes, so these were rated low risk of bias.

** All studies described the type of surgical procedure, so we rated this low risk of bias for all studies.

*** This domain was rated low as we felt it was unlikely another intervention would be initiated at the same time as surgery.

Overall risk of bias for all studies was rated High, as no studies had a control group.

Harms (KQ3)

Pharmacologic Interventions

Table C-23. Harms of pharmacologic interventions: Study characteristics

Study	Study Design	Country	Intervention(s)	N	Study Duration	Funding	Comments
Arzimanoglou et al. (2016)[1581]	Pre/Post	27 sites in Europe	Levetiracetam	101	Mean 5 months	UCB Pharma (manufacturer of the tested medication)	27 sites in Europe
Arican et al. (2018)[1582]	Pre/Post	Turkey	Levetiracetam	92	Median 12 months	No financial support received by authors	Izmir Katip Celebi University, Turkey
Liu et al. (2020)[1584]	RCT	China	Valproate, Valproate + Levetiracetam	100	12 weeks	No financial support received by authors	Xiantao First People's Hospital Affiliated, China
Kim et al. (2009)[1587]	Non-randomized comparative study	South Korea	Topiramate, Carbamazepine	146	Mean 30.7 months	NR	Kyungpook National University Hospital, Daegu, South Korea
Kim et al. (2010)[1597]	Pre/Post	South Korea	Topiramate	81	Average 13.4 months	NR	Chonbuk National University Hospital, South Korea
Manitpisitkul et al. (2013)[1596]	RCT	USA, Brazil, Russia, Ukraine, India	Topiramate (compared doses)	55	6 weeks	Janssen Research & Development (the manufacturer of the medication being tested)	USA, Brazil, Russia, Ukraine, India
Novotny et al. (2010)[1594,1595]	RCT	USA	Topiramate, Placebo	149	20 days	Johnson & Johnson Pharmaceutical Research & Development	Seattle Children's Hospital, USA

Study	Study Design	Country	Intervention(s)	N	Study Duration	Funding	Comments
Piña-Garza et al. (2008)[1588,1589]	Withdrawal RCT	USA	Lamotrigine	204	At least 5 weeks initial open-label phase; double-blind phase 8 weeks; long-term open-label 92% received the medication for at least 24 weeks	GlaxoSmithKline (the manufacturer of the study medication)	12 countries (USA, Australia, Estonia, France, Hungary, Italy, Latvia, Lithuania, The Netherlands, Portugal, Slovakia, Spain)
Sicca et al. (2000)[1590]	Pre/Post	France	Phenytoin	55	3 months	NR	Hospital St. Vincent Du Paul, France
Jackson et al. (2017)[1591]	Pre/Post	USA	Vigabatrin	103	Average 12.1-month followup	Lundbeck, Inc. (manufacturer of the tested medication)	Boston Children's Hospital, USA
Tanritanir et al. (2021)[1592]	Pre/Post	USA	Rufinamide	103	Median 15 months	Investigator initiated grant by Eisai Inc (manufacturer of the tested medication)	Boston Children's Hospital
Yamada et al. (2021)[1593]	Pre/Post	Japan	Stiripentol	95	2 years	Meiji Seika Pharma Co., Ltd	Throughout Japan

RCT = randomized controlled trial; NR = not reported

Table C-24. Harms of pharmacologic interventions: Inclusion criteria

Study	Inclusion Criteria
Arican et al. (2018)[1582]	Diagnosed with epilepsy from January 2014 to January 2017, fewer than 2 years of age at the time levetiracetam was initiated as initial monotherapy and to be followed clinically for at least 6 months. Patients were excluded in the study if they had already received any other antiepileptic drug. Patients were also excluded when seizures had been caused by hypoglycemia and electrolyte disturbances such as hypocalcaemia or hypomagnesaemia.
Arzimanoglou et al. (2016)[1581]	Age 1-11 months diagnosed with epilepsy, received levetiracetam oral solution.

Study	Inclusion Criteria
Liu et al. (2020)[1584]	Treated in Xiantao First People's Hospital Affiliated to Yangtze University (Xiantao, China) from December 2015 to 2018. Patients diagnosed with epilepsy based on the diagnosis criteria that conform to the epilepsy syndrome classification in 2014 National Standardized Diagnosis,Treatment and Scientific Research of Epilepsy, and they received no treatment previously and those without allergy history of medications used in this study. Exclusion criteria: Patients who recently took drugs that affect growth and development as well as glucose and lipid metabolisms, those who used glucocorticoids for a long time, those with severe electrolyte disorder, or those with severe dysfunctions of the liver or kidney.
Kim et al. (2009)[1587]	Under age 2 and initially prescribed either TPM or CBZ at the pediatric neurology clinic, Kyungpook National University Hospital, Daegu, South Korea from January 1, 2000, to December 31, 2003.
Kim et al. (2010)[1597]	Pediatric patients treated at Chonbuk National University Hospital during from July 2004 to July 2006. Fifty-six patients were excluded because of inadequate data, lack of followup, or because they were taking other medications that could induce hypohidrosis.
Manitpisitkul et al. (2013)[1596]	"Infants of either sex, aged 1–24 months and weighing between 3.5–15.5 kg, length at least 49 cm, with at least 41 weeks of gestation, and receiving regular enteral feeding were enrolled. All infants had a diagnosis of partial seizures, based on clinical or electroencephalographic evidence of simple or complex POS, with or without secondary generalization (at least 1 month before screening for infants >6 months of age, or at least 2 weeks before screening for infants <=6 months of age) ; infants could have had other seizure types in addition to POS. Must have been able to tolerate at least 3 mg/kg/day. Infants with additional seizure types were included and all had been receiving at least one concurrent AED for at least 1 month (if >6 months of age), and for >2 weeks (if <=6 months of age) at study entry. A condition of study entry was that seizures were considered to be inadequately controlled." "Infants were excluded if they were exclusively breastfed; could not take oral medications; had a surgically implanted and functioning vagus nerve stimulator; or had a history of febrile seizures or seizures due to an acute medical illness, infantile seizures due to correctable medical condition, or nonepileptic seizures, all within 2 weeks before screening. Infants with abnormal electrocardiography, progressive neurologic disorders, clinically significant uncontrolled medical illness (other than epilepsy), and having history of disturbances of autonomic function, inborn errors of metabolism, allergy or hypersensitivity to any excipients used in topiramate or placebo formulations were excluded. "Infants were not allowed to be on a ketogenic diet, or take furosemide, hydrochlorothiazide, injectable vitamin B6 therapy for pyridoxine-dependent epilepsy, monoamine oxidase inhibitors, felbamate, zonisamide, or any potent carbonic anhydrase inhibitors at the study entry or during the study. Neither immunizations nor cytochrome P450 (CYP) enzyme inducers or inhibitors (except concomitant AEDs) were permitted from the beginning of screening to the end of the open-label core treatment phase."

Study	Inclusion Criteria
Novotny et al. (2010)[1594,1595]	"Infants of either sex, aged 1–24 months, inclusive, of at least 41 weeks of gestational age, weighing at least 3.5 kg but <15.5 kg, length at least 49 cm, and receiving regular enteral feeding were enrolled. At enrollment, infants needed to have a diagnosis of POS, based on clinical or EEG evidence, with or without secondary generalization (at least 1 month before for infants older than 6 months, and at least 2 weeks before for infants aged 6 months or younger), a CT or MRI scan to confirm the absence of a progressive lesion (lesions of tuberous sclerosis and Sturge-Weber syndrome were allowed), and an EKG with no “abnormal, clinically significant” interpretations as made by the central reader. Infants must have been receiving at least 1 concurrent marketed AED other than topiramate for 1 month or more for infants older than 6 months and for more than 2 weeks for infants aged 6 months or younger. The existing treatment was concluded by the investigator to be inadequate in controlling seizures if infants, at optimized doses of the AEDs, had at least 1 seizure in the 4 weeks before screening. In addition, the AED must have been unchanged for at least 5 half-lives before screening. Infants were excluded if they could not take oral medications; had a surgically implanted and functioning vagus nerve stimulator; had epilepsy surgery within 3 months before screening; or had febrile seizures, seizures due to an acute medical illness, or nonepileptic seizures within 2 weeks before the first day of screening. Infants with progressive neurologic disorders, uncontrolled medical illness, disturbances of autonomic function, inborn errors of metabolism, and known hypersensitivity to topiramate were also excluded. Infants with status epilepticus (defined as 30 minutes of continuous motor seizures) in the 2 weeks before, infants who had received more than 4 courses of rescue treatments (such as diazepam) in the month before the first day of screening, and infants using 3 or more concurrent AEDs were excluded from the double-blind phase. Infants who met all inclusion criteria and had in addition at least 4 seizures in the 2 weeks before the first day of screening were qualified for baseline 48-hour vEEG. Infants with evidence of at least 2 countable electroclinical POS seizures in the 48-hour vEEG were eligible for entry into the double-blind phase."
Piña-Garza et al. (2008)[1588,1589]	Initial trial: Required at least a 40% reduction in seizures between the historical baseline phase and the last 4 weeks of the optimization period with lamotrigine to be randomly assigned to the double-blind phase. Male or female infants aged 1 month (based on a 44-week conceptional age) to 24 months diagnosed with partial epilepsy uncontrolled by at least 1 ASM, had a history of at least 4 recurrent partial seizures (i.e., simple, complex, or evolving to secondarily generalized seizures) per month as extrapolated from a 1-week historic observation period immediately before initiation of study medication; had clinical laboratory values within normal limits at screening; had no underlying chronic metabolic abnormalities that could cause or confound the assessment of seizures; and, if they were on non– enzyme-inducing ASM at study entry, weighed at least 6.7 kg. Exclusion criteria included diagnosis of severe, progressive myoclonus; presence of a progressive or unstable neurologic condition that had deteriorated during the month before study entry or seizures unrelated to epilepsy or resulting from drug withdrawal; use of felbamate, adrenocorticotropic hormone, previous use of lamotrigine, more than 2 ASM as maintenance treatment, or valproate with at least1 additional ASM at study entry; use of valproate for less than 6 months or, in the presence of hepatic dysfunction,for more than6 months; having a functioning vagus nerve stimulator; or being on a ketogenic diet. Long-term followup: Either had completed the open-label phase of the initial trial and parent/s guardians judged that continued use of lamotrigine might be beneficial, or were lamotrigine-naive patients who had partial seizures uncontrolled by 1-2 ASM and met the criteria for the initial trial.
Sicca et al. (2000)[1590]	Had been treated at Hospital St. Vincent Du Paul in the first 2 years of life between 1990 and 1997 with PHT for situation-related seizures or seizures occurring in the course of chronic epilepsy, and for whom sufficient data were available regarding clinical history, physical and neurological examinations, drug treatment, laboratory tests (hematology, blood chemistry, AED plasma levels including PHT) and investigations (EEG, brain computed tomography, magnetic resonance imaging).
Jackson et al. (2017)[1591]	Diagnosed with epilepsy, electronic medical record available, treated with vigabatrin at Boston Children's over a 2-year period. Excluded patients whose vigabatrin initiation date was unavailable, whose baseline seizure frequency was unavailable, or whose followup seizure frequency was unavailable, or whose data were incomplete.

Study	Inclusion Criteria
Tanritanir et al. (2021)[1592]	Age 36 months or fewer, received rufinamide for refractory epilepsy (at least 2 prior medications) between June 2010 and June 2018, and had “adequate” clinical information regarding seizure types, frequency, rufinamide dosing, and adverse events. Authors did not define “adequate.”
Yamada et al. (2021)[1593]	Dravet syndrome, received stiripentol between November 2012 and July 2019, and visited the hospital at least once after stiripentol initiation. Authors reported a subgroup analyses of 95 infants age 0-2. To be included in analysis of responders, patients had to have at least 1 seizure during the 4-week baseline period and have sufficient data on seizure frequency during the assessments periods (did not define “sufficient”).

AED – Anti-epileptic drug; CBA – Carbamazepine; EEG -Electroencephalography; TPM – Topiramate; POS - NR = not reported

Table C-25. Harms of pharmacologic interventions: Intervention and patient characteristics

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior Treatments	Seizure Types
Arican et al. (2018)[1582]	Levetiracetam	Initially 10 mg/kg/day titrated up to 60 mg/kg/day. 26% ended at <30 mg/kg/day, 52% took 30-40 mg/kg/day, and the other 22% took >40 mg/kg/day.	92	52% female	NR	Median 6 months (IQR 1-10)	Structural 21%, metabolic 11%, genetic 9%, infectious 3%, unknown 56%	No other prior ASMs. Those sufficiently controlled did not receive additional ASMs. During the study, 31 patients were not sufficiently controlled and 30/31 received at least 1 of 11 additional ASMs (%'s not reported).	Focal 58%, generalized 42%

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior Treatments	Seizure Types
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Mean daily dose 46 mg/kg/day (SD 16)	101	51% female	NR	Mean 6 months (SD 3)	Idiopathic focal 5%, temporal lobe epilepsy 12%, frontal lobe epilepsy 20%, occipital lobe epilepsy 5%, parietal lobe epilepsy 11%, Idiopathic generalized 7%, generalized benign neonatal familial convulsions 2%, generalized benign neonatal convulsions 1%, other generalized idiopathic 4%, West 19.8%, early infantile epileptic encephalopathy with suppression burst 1%, generalized symptomatic nonspecific etiology 1%, other symptomatic generalized epilepsy 3%	Prior ASMs leveltiracetam 35%, phenobarbital 31%, vigabatrin 11%. Concomitant ASMs during the study were vigabatrin 34%, phenobarbital 26%, valproate sodium 23%, and diazepam 20%.	25% focal simple, 43% focal complex, 34% partial evolving to secondary generalized, 1% generalized atypical absence, 8% generalized myoclonic, 7% generalized clonic , 21% generalized tonic, 17% generalized tonic clonic, 1% generalized atonic, 15% unclassified

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior Treatments	Seizure Types
Liu et al. (2020)[1584]	Valproate	Initally 40 mg/kg/day and titrated to a maximum of 50 mg/kg/day, with 3 courses (30 days per course)	50	50% female	NR	2 years (SD 1.1)	NR	No prior treatments permitted. Did not report whether patients received concomitant treatments	NR
Liu et al. (2020)[1584]	Valproate + Levetiracetam	Valproate initally 40 mg/kg/day and titrated to a maximum of 50 mg/kg/day, with 3 courses (30 days per course). Also received levetiracetam initially 20 mg/kg/day and increased once every 5-7 days to a maximum of 30 mg/kg/day.	50	48% female	NR	2 years (SD 1.3)	NR	No prior treatments permitted. Did not report whether patients received concomitant treatments	NR
Kim et al. (2009)[1587]	Carbamazepine	Initial 5-10 mg/kg/day and increased weekly in increments of 5-10/mg/kg/day to a maximum of 30.	105	46% female	NR	8.4 months (SD 5.6)	32% had presence of underlying pathology	No prior treatments permitted. Did not report whether patients received concomitant treatments	44% partial, 47% generalized, 10% unclassified

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior Treatments	Seizure Types
Kim et al. (2009)[1587]	Topiramate	Initial 0.5-1 mg/kg/day and increased weekly in increments of 1/mg/kg/day to a maximum of 3-9.	41	54% female	NR	10 months (SD 6.4)	46% had presence of underlying pathology	No prior treatments permitted. Did not report whether patients received concomitant treatments	20% partial, 71% generalized, 10% unclassified
Kim et al. (2010)[1597]	Topiramate	Topiramate dosing started at 1 mg/kg/d for the first week, then titrated over two-week intervals to a maximum of 5 mg/kg/d. Of the full patient group (N=151), 52 were on topiramate monotherapy and 99 on polytherapy	81	53% female (based on the overall N=151)	NR	All <=12 months old (no other information reported) for the data we extracted	NR	For overall enrolled (N=151), additional ASMs were carbamazepine (36%), valproate (33%), clobazam (19%), lamotrigine (10%), rivotril (8%), vigabatrin (6%), oxcarbazepine (5%), phenytoin (3%), and ativan (3%)	NR
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Weekly dose escalation to the target dose. Oral or sprinkle formulation	14	57% female	79% White, 7% Black, 14% Asian	11 months (SD 5.4)	NR	Concomitant ASMs: Enzyme inducer 29%, Enzyme inhibitor 46%, Enzyme inhibitor and inducer 15%, Neutral 13%	71% partial, 50% partial evolving into secondary generalized, 7% tonic, 7% infantile spasm, 7% other

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior Treatments	Seizure Types
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Weekly dose escalation to the target dose. Oral or sprinkle formulation	13	23% female	85% White, 8% Black, 8% Asian	12 months (SD 5.5)	NR	Concomitant ASMs: Enzyme inducer 29%, Enzyme inhibitor 46%, Enzyme inhibitor and inducer 23%, Neutral 0%	54% partial, 38% partial evolving into secondary generalized, 15% tonic, 31% infantile spasm, 8% other
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Weekly dose escalation to the target dose. Oral or sprinkle formulation	13	53% female	77% White, 8% Black, 15% Asian	12 months (SD 6.7)	NR	Concomitant ASMs: Enzyme inducer 36%, Enzyme inhibitor 38%, Enzyme inhibitor and inducer 8%, Neutral 13%	69% partial, 62% partial evolving into secondary generalized, 8% tonic, 15% infantile spasm, 0% other
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Weekly dose escalation to the target dose. Oral or sprinkle formulation	15	33% female	73% White, 7% Black, 20% Asian	11 months (SD 6.1)	NR	Concomitant ASMs: Enzyme inducer 43%, Enzyme inhibitor 46%, Enzyme inhibitor and inducer 15%, Neutral 7%	73% partial, 13% partial evolving into secondary generalized, 7% tonic, 27% infantile spasm, 13% other

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior Treatments	Seizure Types
Novotny et al. (2010)[1594,1595]	Placebo	Added to current medications	37	38% female	70% white, 3% Black, 24% Asian, 3% other	Mean 13 months (SD 7.6)	NR	Required to already be on at least one concurrent marketed medication for seizures. Across groups, the most frequently used ASMs at baseline were valproic acid (56%), phenobarbital (29%), and carbamazepine (17%).	100% Partial, and across groups 13% also were having generalized seizures
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Added to current medications. Started at 3 mg/kg/day and titrated every 3 days to a maximum of 5 mg/kg/d or the maximum tolerated dose. Liquid or sprinkle formulation.	38	42% female	66% white, 3% Black, 18% Asian, 13% other	Mean 13 months (SD 7.6)	NR	Required to already be on at least one concurrent marketed medication for seizures. Across groups, the most frequently used ASMs at baseline were valproic acid (56%), phenobarbital (29%), and carbamazepine (17%).	100% Partial, and across groups 13% also were having generalized seizures

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior Treatments	Seizure Types
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Added to current medications. Started at 3 mg/kg/day and titrated every 3 days to a maximum of 15 mg/kg/d or the maximum tolerated dose. Liquid or sprinkle formulation.	37	49% female	51% white, 3% Black, 30% Asian, 16% other	Mean 12 months (SD 6.2)	NR	Required to already be on at least one concurrent marketed medication for seizures. Across groups, the most frequently used ASMs at baseline were valproic acid (56%), phenobarbital (29%), and carbamazepine (17%).	100% Partial, and across groups 13% also were having generalized seizures
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Added to current medications. Started at 3 mg/kg/day and titrated every 3 days to a maximum of 25 mg/kg/d or the maximum tolerated dose. Liquid or sprinkle formulation.	37	38% female	57% white, 5% Black, 19% Asian, 19% other	Mean 10 months (SD 5.2)	NR	Required to already be on at least one concurrent marketed medication for seizures. Across groups, the most frequently used ASMs at baseline were valproic acid (56%), phenobarbital (29%), and carbamazepine (17%).	100% Partial, and across groups 13% also were having generalized seizures

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior Treatments	Seizure Types
Piña-Garza et al. (2008)[1588,1589] initial open label	Lamotrigine open label phase	Maximum maintenance dose 5.1 mg/kg/day for those on either valproate or a non-enzyme-inducing AS<, or 15.6 mg/kg/day for those on enzyme-inducing ASMs.	177	48% female	84% White, 7% Black, 5% American Hispanic, 1% Asian, 2% Other	Median 13.2 months	Symptomatic 59%, Idiopathic 40%, Missing 1%	All had previously attempted 1 ASM. The concomitant ASM was enzyme inducing in 71% and not enzyme inducing or was valproate in 29%.	Simple partial 24%, complex partial 67%, Secondarily generalized 44%, generalized 26%
Piña-Garza et al. (2008)[1588,1589] withdrawal RCT	Lamotrigine	Maximum maintenance dose 5.1 mg/kg/day for those on either valproate or a non-enzyme-inducing ASM, or 15.6 mg/kg/day for those on enzyme-inducing ASMs.	19	37% female	89% White, 5% American Hispanic, 5% Other	Median 13.5 months	Symptomatic 84%, Idiopathic 16%	All had previously attempted 1 ASM. The concomitant ASM was enzyme inducing in 68% and not enzyme inducing or was valproate in 32%.	Simple partial 42%, complex partial 53%, Secondarily generalized 37%, generalized 26%
Piña-Garza et al. (2008)[1588,1589] long term open label	Lamotrigine	Maximum maintenance dose 5.1 mg/kg/day for those on either valproate or a non-enzyme-inducing ASM, or 15.6 mg/kg/day for those on enzyme-inducing ASMs.	204	44% female	84% White, 4%, Black, 7% American Hispanic, 1% Asian, 4% Other	Mean 15.9 months	NR	The concomitant ASM was enzyme-inducing in 59%, not enzyme-inducing in 30%, and was valproate in 11%.	Simple partial 27%, complex partial 62%, secondarily generalized 45%, generalized 25%, partial only 75%, generalized only 1%, both partial and generalized 23%

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior Treatments	Seizure Types
Sicca et al. (2000)[1590]	Phenytoin	Oral treatment (N=33 had started on long-term oral administration after intravenous PHT, and the other N=22 had only received oral administration).	55	For the full N=82 enrolled: 51% female	NR	For the full N=82 enrolled: mean 7.4 months	For the full N=82 enrolled: Hypoxic-ischaemic 13%, Cortical dysplasia 10%, Acute cerebral vasculopathy 9%, Tuberous sclerosis 5%, Meningitis 4%, Viral encephalopathy 2%, Multiple cerebral malformation 2%, Peroxisomal disease 2%, Mitochondrial encephalopathy 2%, Other 11%, Not identified 39%	Prior treatments not reported. Concomitant treatments in 93%, most frequently vigabatrin, carbamazepine (CBZ), clonazepam, clobazam, phenobarbital (PB) and valproate (VPA) (did not report % of patients for each medication)	Generalized epilepsy 51%, partial epilepsy 49%

Study	Intervention	Treatment Details	N	Sex	Race	Age at Intervention	Seizure Etiologies	Prior Treatments	Seizure Types
Jackson et al. (2017)[1591]	Vigabatrin	The median dose at first follow-up was 100 mg/kg per day (IQR 79.4–125) and at last follow-up was 93.8 mg/kg per day (IQR 54–128.6).	103	53% female	NR	Mean 8 months (IQR 5-15)	Structural/metabolic 49.5%, TSC 24%, Malformation of cortical development 18%, other 8%	Concomitant treatments were Levetiracetam in 35%, Topiramate in 31.1%, Phenobarbital in 25.2%, Clonazepam in 12.6%, Clobazam in 10.7%, Zonisamide in 9.7%, Oxcarbazepine in 6.8%, Valproic acid in 5.8%, Phenytoin in 1.9%, Rufinamide in 1.9%, Lacosamide in 1.9%, Lorazepam in 1.9%, Lamotrigine in 0.97%, Tiagabine in 0.97%, Gabapentin in 0.97%, Pyridoxine in 12%, Steroid in 11%, Ketogenic diet in 2%	91% "epileptic spasm", 15% focal, 10% generalized tonic, 5% generalized myoclonic, 5% generalized tonic-clonic, 4% generalized atonic, and 1% generalized absence

ASM = Anti-seizure medication; IQR = interquartile range; NR = not reported; SD = standard deviation

Table C-26. Harms of pharmacologic interventions: Data

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Arican et al. (2018)[1582]	Levetiracetam	Behavioral side effects	Median 12 months	0% (0/92)	None
Arican et al. (2018)[1582]	Levetiracetam	Biochemical side effects	Median 12 months	0% (0/92)	None
Arican et al. (2018)[1582]	Levetiracetam	Hematological side effects	Median 12 months	0% (0/92)	None
Arican et al. (2018)[1582]	Levetiracetam	Irritability	Median 12 months	5% (5/92)	None
Arican et al. (2018)[1582]	Levetiracetam	Withdrawal due to AE	Median 12 months	0% (0/92)	None
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Adverse event requiring dose change	Mean 5 months	10% (10/101)	Table 3
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Bronchiolitis	Mean 5 months	3% (3/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Bronchitis	Mean 5 months	10% (10/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Constipation	Mean 5 months	3% (3/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Convulsion	Mean 5 months	10% (10/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Death unrelated to study drug according to investigators	Mean 5 months	6% (6/101)	Table 3
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Diarrhea	Mean 5 months	6% (6/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Drug-related adverse event	Mean 5 months	5% (5/101)	Table 3
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Ear infection	Mean 5 months	3% (3/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Epilepsy	Mean 5 months	3% (3/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Gastroenteritis	Mean 5 months	4% (4/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Gastro-oesophageal reflux disease	Mean 5 months	3% (3/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Hypotonia	Mean 5 months	2% (2/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Infantile spasm	Mean 5 months	3% (3/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Irritability	Mean 5 months	4% (4/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Lower respiratory tract infection	Mean 5 months	2% (2/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Nasopharyngitis	Mean 5 months	4% (4/101)	Table 4

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Fever	Mean 5 months	8% (8/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Respiratory disorder	Mean 5 months	2% (2/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Respiratory distress	Mean 5 months	2% (2/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Serious adverse event (any)	Mean 5 months	32% (32/101)	Table 3
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Severe treatment related adverse event	Mean 5 months	12% (12/101)	Table 3
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Upper respiratory tract infection	Mean 5 months	2% (2/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Urinary tract infection	Mean 5 months	2% (2/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Viral infection	Mean 5 months	2% (2/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Vomiting	Mean 5 months	3% (3/101)	Table 4
Arzimanoglou et al. (2016)[1581]	Levetiracetam	Withdrawal due to AE	Mean 5 months	7% (7/101)	Table 3. Specific events were respiratory disorder (2), respiratory distress and infantile spasm (2), irritability (1), lower respiratory tract infection (1), and psychomotor retardation and respiratory failure (1).
Liu et al. (2020)[1584]	Valproate	Gastrointestinal reaction	12 weeks	8% (4/50)	Table III
Liu et al. (2020)[1584]	Valproate + Levetiracetam	Gastrointestinal reaction	12 weeks	4% (2/50)	Table III
Liu et al. (2020)[1584]	Valproate	Nausea	12 weeks	10% (5/50)	Table III
Liu et al. (2020)[1584]	Valproate + Levetiracetam	Nausea	12 weeks	2% (1/50)	Table III
Liu et al. (2020)[1584]	Valproate	Rash	12 weeks	4% (2/50)	Table III
Liu et al. (2020)[1584]	Valproate + Levetiracetam	Rash	12 weeks	2% (1/50)	Table III
Liu et al. (2020)[1584]	Valproate	Sleepiness	12 weeks	6% (3/50)	Table III

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Liu et al. (2020)[1584]	Valproate + Levetiracetam	Sleepiness	12 weeks	2% (1/50)	Table III
Kim et al. (2009)[1587]	Carbamazepine	Anhidrosis	6 months	0% (0/105)	Figure 4
Kim et al. (2009)[1587]	Topiramate	Anhidrosis	6 months	2% (1/41)	Figure 4
Kim et al. (2009)[1587]	Carbamazepine	Diarrhea	6 months	1% (1/105)	Figure 4
Kim et al. (2009)[1587]	Topiramate	Diarrhea	6 months	0% (0/41)	Figure 4
Kim et al. (2009)[1587]	Carbamazepine	Hair loss	6 months	1% (1/105)	Figure 4
Kim et al. (2009)[1587]	Topiramate	Hair loss	6 months	0% (0/41)	Figure 4
Kim et al. (2009)[1587]	Carbamazepine	Hyperactivity	6 months	0% (0/105)	Figure 4
Kim et al. (2009)[1587]	Topiramate	Hyperactivity	6 months	2% (1/41)	Figure 4
Kim et al. (2009)[1587]	Carbamazepine	Liver enzyme	6 months	2% (2/105)	Figure 4
Kim et al. (2009)[1587]	Topiramate	Liver enzyme	6 months	0% (0/41)	Figure 4
Kim et al. (2009)[1587]	Carbamazepine	Nausea/vomiting	6 months	1% (1/105)	Figure 4
Kim et al. (2009)[1587]	Topiramate	Nausea/vomiting	6 months	2% (1/41)	Figure 4
Kim et al. (2009)[1587]	Carbamazepine	Poor oral intake	6 months	1% (1/105)	Figure 4
Kim et al. (2009)[1587]	Topiramate	Poor oral intake	6 months	2% (1/41)	Figure 4
Kim et al. (2009)[1587]	Carbamazepine	Psychomotor retardation	6 months	0% (0/105)	Figure 4
Kim et al. (2009)[1587]	Topiramate	Psychomotor retardation	6 months	17% (7/41)	Figure 4
Kim et al. (2009)[1587]	Carbamazepine	Skin rash	6 months	4% (4/105)	Figure 4
Kim et al. (2009)[1587]	Topiramate	Skin rash	6 months	0% (0/41)	Figure 4
Kim et al. (2009)[1587]	Carbamazepine	Sleepiness	6 months	10% (11/105)	Figure 4
Kim et al. (2009)[1587]	Topiramate	Sleepiness	6 months	2% (1/41)	Figure 4
Kim et al. (2009)[1587]	Carbamazepine	Withdrawal due to AE	6 months	23% (24/105)	Figure 5. Did not report the specific events leading to withdrawal.
Kim et al. (2009)[1587]	Topiramate	Withdrawal due to AE	6 months	12% (5/41)	Figure 5. Did not report the specific events leading to withdrawal.

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Kim et al. (2010)[1597]	Topiramate	Hypohydrosis	Average 13.4 months	48% (39/81)	From Table 2
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Treatment-emergent serious adverse event	Average 13.4 months	14% (2/14)	Infections or convulsions aggravated
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Treatment-emergent serious adverse event	Average 13.4 months	0% (0/13)	Infections or convulsions aggravated
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Treatment-emergent serious adverse event	Average 13.4 months	15% (2/13)	Infections or convulsions aggravated
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Treatment-emergent serious adverse event	Average 13.4 months	13% (2/15)	Infections or convulsions aggravated
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Anorexia	Average 13.4 months	7% (1/14)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Anorexia	Average 13.4 months	8% (1/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Anorexia	Average 13.4 months	8% (1/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Anorexia	Average 13.4 months	20% (3/15)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Bronchitis	Average 13.4 months	0% (0/14)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Bronchitis	Average 13.4 months	0% (0/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Bronchitis	Average 13.4 months	8% (1/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Bronchitis	Average 13.4 months	13% (2/15)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Coughing	Average 13.4 months	7% (1/14)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Coughing	Average 13.4 months	8% (1/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Coughing	Average 13.4 months	0% (0/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Coughing	Average 13.4 months	13% (2/15)	Table 4

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Diarrhea	Average 13.4 months	0% (0/14)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Diarrhea	Average 13.4 months	8% (1/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Diarrhea	Average 13.4 months	0% (0/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Diarrhea	Average 13.4 months	27% (4/15)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Fever	Average 13.4 months	7% (1/14)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Fever	Average 13.4 months	15% (2/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Fever	Average 13.4 months	0% (0/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Fever	Average 13.4 months	33% (5/15)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Nephrolithiasis	Average 13.4 months	0% (0/14)	None
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Nephrolithiasis	Average 13.4 months	0% (0/13)	None
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Nephrolithiasis	Average 13.4 months	0% (0/13)	None
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Nephrolithiasis	Average 13.4 months	0% (0/15)	None
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Otitis media	Average 13.4 months	7% (1/14)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Otitis media	Average 13.4 months	0% (0/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Otitis media	Average 13.4 months	0% (0/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Otitis media	Average 13.4 months	13% (2/15)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Rhinitis	Average 13.4 months	0% (0/14)	Table 4

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Rhinitis	Average 13.4 months	8% (1/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Rhinitis	Average 13.4 months	0% (0/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Rhinitis	Average 13.4 months	20% (3/15)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Somnolence	Average 13.4 months	0% (0/14)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Somnolence	Average 13.4 months	15% (2/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Somnolence	Average 13.4 months	8% (1/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Somnolence	Average 13.4 months	20% (3/15)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Upper resp tract inf	Average 13.4 months	0% (0/14)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Upper resp tract inf	Average 13.4 months	8% (1/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Upper resp tract inf	Average 13.4 months	15% (2/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Upper resp tract inf	Average 13.4 months	38% (5/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Viral infection	Average 13.4 months	0% (0/14)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Viral infection	Average 13.4 months	0% (0/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Viral infection	Average 13.4 months	23% (3/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Viral infection	Average 13.4 months	7% (1/15)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Vomiting	Average 13.4 months	7% (1/14)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Vomiting	Average 13.4 months	8% (1/13)	Table 4

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Vomiting	Average 13.4 months	15% (2/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Vomiting	Average 13.4 months	20% (3/15)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Weight decrease	Average 13.4 months	0% (0/14)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Weight decrease	Average 13.4 months	0% (0/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Weight decrease	Average 13.4 months	0% (0/13)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Weight decrease	Average 13.4 months	13% (2/15)	Table 4
Manitpisitkul et al. (2013)[1596]	Topiramate 3 mg/kg/d	Withdrawal due to AE	Average 13.4 months	0% (0/14)	Figure 1
Manitpisitkul et al. (2013)[1596]	Topiramate 5 mg/kg/d	Withdrawal due to AE	Average 13.4 months	8% (1/13)	Figure 1. Did not report the specific event(s) leading to this 1 withdrawal.
Manitpisitkul et al. (2013)[1596]	Topiramate 15 mg/kg/d	Withdrawal due to AE	Average 13.4 months	15% (2/13)	Figure 1. Did not report the specific events leading to these 2 withdrawals.
Manitpisitkul et al. (2013)[1596]	Topiramate 25 mg/kg/d	Withdrawal due to AE	Average 13.4 months	0% (0/15)	Figure 1
Novotny et al. (2010)[1594,1595]	Placebo	Treatment-emergent serious adverse event	20 days	8% (3/37)	NR specifics
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Treatment-emergent serious adverse event	20 days	8% (3/38)	NR specifics
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Treatment-emergent serious adverse event	20 days	8% (3/37)	NR specifics
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Treatment-emergent serious adverse event	20 days	8% (3/37)	NR specifics
Novotny et al. (2010)[1594,1595]	Placebo	Acidosis	20 days	0% (0/37)	Estimated from Figure 3

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Acidosis	20 days	0% (0/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Acidosis	20 days	5% (2/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Acidosis	20 days	3% (1/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Anorexia	20 days	5% (2/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Anorexia	20 days	11% (4/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Anorexia	20 days	11% (4/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Anorexia	20 days	16% (6/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Ataxia	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Ataxia	20 days	3% (1/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Ataxia	20 days	5% (2/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Ataxia	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Bronchitis	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Bronchitis	20 days	8% (3/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Bronchitis	20 days	3% (1/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Bronchitis	20 days	8% (3/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Bronchospasm	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Bronchospasm	20 days	0% (0/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Bronchospasm	20 days	8% (3/37)	Estimated from Figure 3

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Bronchospasm	20 days	5% (2/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Coughing	20 days	5% (2/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Coughing	20 days	5% (2/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Coughing	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Coughing	20 days	11% (4/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Dermatitis	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Dermatitis	20 days	3% (1/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Dermatitis	20 days	5% (2/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Dermatitis	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Diarrhea	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Diarrhea	20 days	3% (1/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Diarrhea	20 days	11% (4/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Diarrhea	20 days	8% (3/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Fever	20 days	11% (4/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Fever	20 days	29% (11/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Fever	20 days	19% (7/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Fever	20 days	19% (7/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Infection viral	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Infection viral	20 days	13% (5/38)	Estimated from Figure 3

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Infection viral	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Infection viral	20 days	8% (3/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Mouth dry	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Mouth dry	20 days	0% (0/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Mouth dry	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Mouth dry	20 days	5% (2/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Nervousness	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Nervousness	20 days	8% (3/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Nervousness	20 days	8% (3/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Nervousness	20 days	3% (1/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Otitus media	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Otitus media	20 days	5% (2/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Otitus media	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Otitus media	20 days	5% (2/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Pharyngitis	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Pharyngitis	20 days	5% (2/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Pharyngitis	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Pharyngitis	20 days	3% (1/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Rhinitis	20 days	0% (0/37)	Estimated from Figure 3

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Rhinitis	20 days	5% (2/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Rhinitis	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Rhinitis	20 days	5% (2/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Saliva increased	20 days	3% (1/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Saliva increased	20 days	0% (0/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Saliva increased	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Saliva increased	20 days	5% (2/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Skin dry	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Skin dry	20 days	5% (2/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Skin dry	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Skin dry	20 days	0% (0/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Somnolence	20 days	8% (3/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Somnolence	20 days	8% (3/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Somnolence	20 days	22% (8/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Somnolence	20 days	16% (6/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Upper respiratory tract infection	20 days	14% (5/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Upper respiratory tract infection	20 days	21% (8/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Upper respiratory tract infection	20 days	22% (8/37)	Estimated from Figure 3

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Upper respiratory tract infection	20 days	22% (8/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Vomiting	20 days	5% (2/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Vomiting	20 days	18% (7/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Vomiting	20 days	8% (3/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Vomiting	20 days	16% (6/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Weight decrease	20 days	3% (1/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Weight decrease	20 days	0% (0/38)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Weight decrease	20 days	5% (2/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Weight decrease	20 days	14% (5/37)	Estimated from Figure 3
Novotny et al. (2010)[1594,1595]	Placebo	Withdrawal due to AE	20 days	5% (2/37)	From Figure 1. Did not report the specific events leading to this withdrawal.
Novotny et al. (2010)[1594,1595]	Topiramate 5 mg/kg/d	Withdrawal due to AE	20 days	3% (1/38)	From Figure 1. Patient got staphylococcemia and died, and authors stated it was unrelated to topiramate.
Novotny et al. (2010)[1594,1595]	Topiramate 15 mg/kg/d	Withdrawal due to AE	20 days	5% (2/37)	From Figure 1. Did not report the specific events leading to this withdrawal.
Novotny et al. (2010)[1594,1595]	Topiramate 25 mg/kg/d	Withdrawal due to AE	20 days	3% (1/37)	From Figure 1. Did not report the specific event(s) leading to this withdrawal.
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Any rash	At least 5 weeks	15% (26/177)	Table 3

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Bronchitis	At least 5 weeks	5% (8/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Complex partial seizure	At least 5 weeks	7% (12/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Constipation	At least 5 weeks	14% (24/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Cough	At least 5 weeks	12% (21/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Dermatitis diaper	At least 5 weeks	6% (11/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Diarrhea	At least 5 weeks	11% (19/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Ear infection	At least 5 weeks	10% (17/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Insomnia	At least 5 weeks	5% (9/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Irritability	At least 5 weeks	10% (17/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Nasal congestion	At least 5 weeks	6% (10/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Nasopharyngitis	At least 5 weeks	16% (29/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Otitis media	At least 5 weeks	11% (20/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Pharyngitis	At least 5 weeks	7% (12/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label phase	Lamotrigine	Pneumonia	At least 5 weeks	5% (8/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open-label	Lamotrigine	Fever	At least 5 weeks	41% (73/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open label phase	Lamotrigine	Serious event: apnea	At least 5 weeks	2% (4/177)	None
Piña-Garza et al. (2008)[1588,1589] initial open label phase	Lamotrigine	Serious event: complex partial seizures	At least 5 weeks	3% (6/177)	None

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Piña-Garza et al. (2008)[1588,1589] initial open label phase	Lamotrigine	Serious event: convulsions	At least 5 weeks	2% (4/177)	None
Piña-Garza et al. (2008)[1588,1589] initial open label phase	Lamotrigine	Serious event: cyanosis	At least 5 weeks	2% (3/177)	None
Piña-Garza et al. (2008)[1588,1589] initial open label phase	Lamotrigine	Serious event: partial seizures with secondary generalization	At least 5 weeks	2% (3/177)	None
Piña-Garza et al. (2008)[1588,1589] initial open label phase	Lamotrigine	Serious event: pneumonia	At least 5 weeks	2% (3/177)	None
Piña-Garza et al. (2008)[1588,1589] initial open label phase	Lamotrigine	Serious event: status epilepticus	At least 5 weeks	2% (3/177)	None
Piña-Garza et al. (2008)[1588,1589] initial open label phase	Lamotrigine	Somnolence	At least 5 weeks	5% (8/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open label phase	Lamotrigine	Teething	At least 5 weeks	12% (22/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open label phase	Lamotrigine	Upper respiratory tract congestion	At least 5 weeks	7% (12/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open label phase	Lamotrigine	Upper respiratory tract infection	At least 5 weeks	19% (33/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open label phase	Lamotrigine	Vomiting	At least 5 weeks	19% (33/177)	Table 3
Piña-Garza et al. (2008)[1588,1589] initial open label phase	Lamotrigine	Withdrawal due to AE	At least 5 weeks	8% (14/177)	Specific events were rash (n=8), myoclonic epilepsy (n=2), and complex partial seizures (n = 2). The other two were not reported.
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Bronchitis	≥24 weeks in 92%	11% (23/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Complex partial seizures	≥24 weeks in 92%	7% (14/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Constipation	≥24 weeks in 92%	16% (33/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Convulsion	≥24 weeks in 92%	6% (13/204)	Table 3

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Cough	≥24 weeks in 92%	19% (39/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Diarrhea	≥24 weeks in 92%	8% (16/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Ear infection	≥24 weeks in 92%	22% (45/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Gastroenteritis	≥24 weeks in 92%	6% (12/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Insomnia	≥24 weeks in 92%	6% (13/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Irritability	≥24 weeks in 92%	17% (35/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Nasopharyngitis	≥24 weeks in 92%	14% (29/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Otitis media	≥24 weeks in 92%	17% (35/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Pharyngitis	≥24 weeks in 92%	8% (16/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Pneumonia	≥24 weeks in 92%	11% (23/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Fever	≥24 weeks in 92%	45% (92/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Rash	≥24 weeks in 92%	13% (27/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Respiratory tract infection	≥24 weeks in 92%	6% (13/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Serious event: Complex partial seizures	≥24 weeks in 92%	6% (12/204)	None
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Serious event: Convulsion	≥24 weeks in 92%	3% (6/204)	None
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Serious event: Dehydration	≥24 weeks in 92%	3% (6/204)	None
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Serious event: Gastroenteritis	≥24 weeks in 92%	3% (6/204)	None

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Serious event: Pneumonia	≥24 weeks in 92%	8% (16/204)	None
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Serious event: Fever	≥24 weeks in 92%	4% (8/204)	None
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Serious event: Status epilepticus	≥24 weeks in 92%	6% (12/204)	None
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Status epilepticus	≥24 weeks in 92%	10% (21/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Teething	≥24 weeks in 92%	13% (27/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Upper respiratory tract congestion	≥24 weeks in 92%	7% (14/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Upper respiratory tract infection	≥24 weeks in 92%	28% (58/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Viral infection	≥24 weeks in 92%	7% (14/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Vomiting	≥24 weeks in 92%	18% (37/204)	Table 3
Piña-Garza et al. (2008)[1588,1589] long-term open label phase	Lamotrigine	Withdrawal due to AE	≥24 weeks in 92%	9% (18/204)	Specific events were pneumonia (n = 4), complex partial seizures (n = 3), status epilepticus (n = 3), rash (n = 3), and fever (n = 2).. The other three were unreported.
Piña-Garza et al. (2008)[1588,1589] RCT portion	Lamotrigine	Cough	8 weeks	11% (2/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Replacement of lamotrigine with placebo	Cough	8 weeks	0% (0/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Lamotrigine	Nasal congestion	8 weeks	11% (2/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Replacement of lamotrigine with placebo	Nasal congestion	8 weeks	5% (1/19)	None

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Piña-Garza et al. (2008)[1588,1589] RCT portion	Lamotrigine	Fever	8 weeks	11% (2/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Replacement of lamotrigine with placebo	Fever	8 weeks	11% (2/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Lamotrigine	Rash (moderate intensity)	8 weeks	5% (1/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Replacement of lamotrigine with placebo	Rash (moderate intensity)	8 weeks	0% (0/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Lamotrigine	Serious event: bronchitis	8 weeks	5% (1/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Replacement of lamotrigine with placebo	Serious event: bronchitis	8 weeks	0% (0/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Lamotrigine	Serious event: status epilepticus	8 weeks	0% (0/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Replacement of lamotrigine with placebo	Serious event: status epilepticus	8 weeks	5% (1/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Lamotrigine	Teething	8 weeks	0% (0/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Replacement of lamotrigine with placebo	Teething	8 weeks	16% (3/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Lamotrigine	Upper respiratory tract infection	8 weeks	11% (2/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Replacement of lamotrigine with placebo	Upper respiratory tract infection	8 weeks	0% (0/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Lamotrigine	Withdrawal due to AE	8 weeks	0% (0/19)	None
Piña-Garza et al. (2008)[1588,1589] RCT portion	Replacement of lamotrigine with placebo	Withdrawal due to AE	8 weeks	0% (0/19)	None

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Sicca et al. (2000)[1590]	Phenytoin	Allergic reaction	3 months	2% (1/55)	None
Sicca et al. (2000)[1590]	Phenytoin	Anorexia	3 months	4% (2/55)	None
Sicca et al. (2000)[1590]	Phenytoin	Ataxia	3 months	9% (5/55)	None
Sicca et al. (2000)[1590]	Phenytoin	Behavior disturbances	3 months	2% (1/55)	None
Sicca et al. (2000)[1590]	Phenytoin	Cognitive disturbances	3 months	4% (2/55)	None
Sicca et al. (2000)[1590]	Phenytoin	Drowsiness	3 months	22% (12/55)	None
Sicca et al. (2000)[1590]	Phenytoin	Gingival hyperplasia	3 months	15% (8/55)	None
Sicca et al. (2000)[1590]	Phenytoin	Hyperactivity	3 months	11% (6/55)	None
Sicca et al. (2000)[1590]	Phenytoin	Loss of weight	3 months	7% (4/55)	None
Sicca et al. (2000)[1590]	Phenytoin	Movement disorders	3 months	7% (4/55)	None
Sicca et al. (2000)[1590]	Phenytoin	Sleep troubles	3 months	15% (8/55)	None
Sicca et al. (2000)[1590]	Phenytoin	Vomiting	3 months	7% (4/55)	None
Jackson et al. (2017)[1591]	Vigabatrin	Anemia	Median 12 months	1% (1/71)	The denominator only includes the N=71 who discontinued vigabatrin
Jackson et al. (2017)[1591]	Vigabatrin	Anorexia	Median 12 months	1% (1/71)	The denominator only includes the N=71 who discontinued vigabatrin
Jackson et al. (2017)[1591]	Vigabatrin	Fatigue	Median 12 months	3% (2/71)	The denominator only includes the N=71 who discontinued vigabatrin
Jackson et al. (2017)[1591]	Vigabatrin	Medication toxicity	Median 12 months	1% (1/71)	The denominator only includes the N=71 who discontinued vigabatrin
Jackson et al. (2017)[1591]	Vigabatrin	Vigabatrin related toxicity	Median 12 months	1% (1/71)	The denominator only includes the N=71 who discontinued vigabatrin
Jackson et al. (2017)[1591]	Vigabatrin	Vision abnormality	Median 12 months	8% (6/71)	The denominator only includes the N=71 who discontinued vigabatrin

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Jackson et al. (2017)[1591]	Vigabatrin	Withdrawal due to AE	Median 12 months	9% (9/103)	Figure 3. Specific events were vision abnormality (n=5), fatigue (1), fatigue and anorexia (1), “possible VBG toxicity” (1), and anemia (1).
Jackson et al. (2017)[1591]	Vigabatrin	Vision abnormality on eye exam	Before vigabatrin	69% (34/49)	Authors attributed these abnormalities to tuberous sclerosis complex, refractive errors, and prior medication..
Jackson et al. (2017)[1591]	Vigabatrin	Vision abnormality on eye exam	During vigabatrin	81% (50/62)	This comprises on the 62 who had electroretinography during vigabatrin. Some had 2+ electroretinographies, and 50 had a vision abnormality on at least one test.
Jackson et al. (2017)[1591]	Vigabatrin	Vision abnormality on eye exam	After vigabatrin	63% (31/49)	None
Tanritanir et al. (2021)[1592]	Rufinamide	Discontinuation due to adverse effects	Median 15 months	15% (15/103)	3 of the 15 discontinuations were due solely to adverse effects, and the other 12 were due to both adverse effects and lack of efficacy.
Tanritanir et al. (2021)[1592]	Rufinamide	Somnolence	Median 15 months	12% (12/103)	None
Tanritanir et al. (2021)[1592]	Rufinamide	Insomnia	Median 15 months	5% (5/103)	None
Tanritanir et al. (2021)[1592]	Rufinamide	Nausea	Median 15 months	7% (7/103)	None
Tanritanir et al. (2021)[1592]	Rufinamide	Vomiting	Median 15 months	3% (3/103)	None
Tanritanir et al. (2021)[1592]	Rufinamide	Mood-behavioral change	Median 15 months	2% (2/103)	None
Tanritanir et al. (2021)[1592]	Rufinamide	Irritability	Median 15 months	10% (10/103)	None

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Tanritanir et al. (2021)[1592]	Rufinamide	Appetite change	Median 15 months	4% (4/103)	None
Tanritanir et al. (2021)[1592]	Rufinamide	Weight loss	Median 15 months	1% (1/103)	None
Tanritanir et al. (2021)[1592]	Rufinamide	Diplopua	Median 15 months	1% (1/103)	None
Tanritanir et al. (2021)[1592]	Rufinamide	Temporary blood lactic acid level elevation	Median 15 months	1% (1/103)	None
Yamada et al. (2021)[1593]	Stiripentol	Any adverse drug reaction	Two years	61% (58/95)	Physicians in charge determined that all 58 had a causal relationship to stiripentol (either "clearly" or "probably" or possibly"). Authors did not report the specific adverse events experienced by those age 0-2.
Yamada et al. (2021)[1593]	Stiripentol	Death due to liver damage	Two months	1% (1/95)	Physicians in charge determined that the causal relationship to stiripentol was "possible", and additional possible causes were valproate and clobazam

NR: not reported

Dietary Interventions

Table C-27. Harms of dietary interventions: Study characteristics

Study	Study Design	Country	Interventions	n	Comparator	n	Study Duration	Funding	Comments
Kim et al. 2019[1600]	Pre/Post	USA	Ketogenic Diet	49	NA	NA	3 months	None	Conducted at Lurie Children's Hospital. Patients with West Syndrome excluded per protocol.
Dressler et al. 2015[355]	Pre/Post	Austria	Ketogenic Diet (classic)	58	NA	NA	18 months	None.	Conducted at Medical University Vienna.

Study	Study Design	Country	Interventions	n	Comparator	n	Study Duration	Funding	Comments
Liu et al. 2021[1602]	Pre/Post	China	Ketogenic Diet (classic)	41	NA	NA	12 months	NR.	Conducted at Children's Hospital of Chongqing Medical University, Chongqing, China.
El-Rashidy et al. 2013[1603]	RCT	Egypt	Ketogenic Diet (classic)	10	Modified Atkins Diet ASM Polytherapy	15 15	> 6 months	Children's hospital, Faculty of Medicine, Ain Shams University	Conducted at Children's Hospital Ain Shams University

NA = not applicable

Table C-28. Harms of dietary interventions: Patient characteristics

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Kim et al. 2019[1600]	Under the age of 3 years with medically intractable epilepsy, defined as persistent seizures despite the use of two or more appropriate anticonvulsants at therapeutic doses.	Ketogenic Diet	49	NRFS	Mean 1.4 ± 0.8	Non West Syndrome	Median 4 anticonvulsants.	None
Dressler et al. 2015[355]	Included were all children with complete clinical data and observation periods of at least 3 months after initiation of the KD.	Ketogenic Diet (classic)	58	NRFS	0.68 ± 0.45 years	NRFS	2.47 ± 2 ASMs	None

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Liu et al. 2021[1602]	Infants born full terms aged 6 to 36 months with refractory epilepsy who took two or more anticonvulsants. Patients with organ failures, chronic infectious diseases, or thyroid disorders were excluded.	• Ketogenic Diet (classic)	•41	• 23 males 18 females	•20.51 ± 4.05 months	NR	2 or more anticonvulsants	None
El-Rashidy et al. 2013[1603]	Patients diagnosed with symptomatic intractable epilepsy according to the definition of Beleza.	• Ketogenic Diet (classic) • Modified Atkins Diet Normal Diet	•10 •15 15	•5 males 5 females •8 males 7 females •8 males 7 females	•26 ± 0.9 months •27.13 ± 6.63 months 25.73 ± 6.35 months	•11 post-anoxic, 3 post-traumatic, 7 post-hemorrhagic. 3 focal, 4 general, 2 infantile spasm, 1 early infantile myoclonic encephalopathy. 3 post-anoxic, 4 post-hemorrhagic, 2 Tuberous sclerosis, 1 syndromic epilepsy. 4 focal, 11 general.	ASM polytherapy for all	None

KD = ketogenic diet; NRFS = not reported for the subgroup; ASM = antiseizure drugs

Table C-29. Harms of dietary interventions: Treatment characteristics

Study	Intervention	n	Treatment Details	Seizure Measurement Methods	Comments
Kim et al. 2019[1600]	Ketogenic Diet	49	KD was initiated at a ratio of 1:1 (fat grams: carbohydrate + protein grams) without a fast as an inpatient in the hospital. The keto ratio was increased daily, reaching up to 3:1 on day 3. On day 4, patients were discharged home at the ratio of 3:1 with full calories. Fluids were not restricted.	Medical records, retrospective study.	None
Dressler et al. 2015[355]	Ketogenic Diet (classic)	58	According to the Johns Hopkins protocol without fasting and fluid restriction. The ketogenic ratio in infants during the first year of life is usually 3:1 or 2.5:1. In older children the ketogenic ratio used is 4:1.	Parental seizure diaries and EEG	None
Liu et al. 2021[1602]	Ketogenic Diet (classic)	•41	Classic KD, unspecified.	NR	None
El-Rashidy et al. 2013[1603]	• Ketogenic Diet (classic) • Modified Atkins Diet • • • Normal Diet	•10 •15 15	•The classic 4:1 KD was provided as a formula. •Modified Atkins diet consisted of a nearly balanced diet (60% fat, 30% protein, and 10% carbohydrates by weight) without restrictions. Normal accustomed diet with anti-epileptic polytherapy.	Seizure frequency and severity recorded during outpatient visits, details not specified.	All groups concurrently on ASM: valproic acid and carbamazepine ± clonazepam

EEG = electroencephalography

Table C-30. Harms of dietary interventions: Harms outcomes

Study	Intervention	Adverse Events
Kim et al. 2019[1600]	Ketogenic Diet	2/109 withdrew due to AE (1 behavioral food refusal, and 1 persistent acidosis). Constipation 32% (35/109) Decreased HC03 level 33% (36/109) Vomiting or reflux 20% (22/109) Low free carnitine level 8% (9/109) Feeding difficulty 6% (6/109) Kidney stone 3% (3/109) Transient hypoglycemia 2% (2/109) Other 6% (7/109)
Dressler et al. 2015[355]	Ketogenic Diet (classic)	Side effects (unspecified): 29 Difficulties introducing solid food: 16
Liu et al. 2021[1602]	Ketogenic Diet (classic)	The 41 patients were in three age groups: Group A (age 6-12) N=9, Group B (age 12-18 months), and Group C (age 18-24 months). BMI-for-age z score (age groups combined by the EPC): • Baseline mean 0.49 (SD 2.36) • 1 month mean 0.14 (SD 1.98) • 3 month mean 0.06 (SD 1.83) • 6 month mean 0.16 (SD 1.71) • 12 month mean 0.35 (SD 1.4). Assuming a prepost correlation of 0.5, the reduction in BMI-for-age z score was not statistically significantly different from baseline at any follow-up timepoint (statistical tests performed by the EPC). Authors also reported that at baseline 17% of patients (7/41) were underweight (defined as weight-for-age z score <-2), 22% of patients (9/41) were stunted (defined as height-for-age z score <-2), 20% of patients (8/41) were wasting (defined as BMI-for-age z score <-2), and 17% of patients (7/41) were overweight or obese (defined as weight-for-age z score >2). Authors stated that "Over the course of 12 months of KDT, the overall prevalence of underweight, stunting, wasting, and overweight/obesity in children in groups A and B decreased. The prevalence of underweight and stunting in group C increased by 5.6% and 11.1%, respectively. However, those changes were not statistically significant (p>0.05). In addition, the prevalence of overweight/ obesity in the three groups of children decreased significantly, and the prevalence of overweight/obesity among the three groups of children decreased to 0%, 0% and 5.6%, respectively."Therefore the rate of overweight/obese reduced from 17% (7/41) to 2% (1/41). The EPC performed McNemar's test on these percentages (assuming that the one child who was overweight/obese at followup had also been overweight/obese at baseline), and this comparison was statistically significant (McNemar chisquare=6, p=0.0313). For underweight/stunting/wasting, data were not reported in a way for the EPC to combine the three age groups to determine whether any of the percentages statistically significantly changed for the full group while on the KD.

Study	Intervention	Adverse Events
El-Rashidy et al. 2013[1603]	• Ketogenic Diet (classic) • Modified Atkins Diet Normal Diet	Withdrawals due to diet intolerance: KD 20% (2/10) and MAD 13% (2/15). The two MAD dropouts suffered "significant" weight loss. Vomiting: KD: 0% (0/10), MAD: 27% (4/15) Constipation: KD: 20% (2/10), MAD: 13% (2/15) Diarrhea: KD: 10% (1/10), MAD: 13% (2/15) Dysphagia: KD: 12.5% (1/10), MAD: 20% (3/15) Authors stated that "all these medical complications responded to simple dietary advices and minor medications as anti-emetics and H2 blockers"

EEG = electroencephalography

Surgical Interventions

Table C-31. Harms of surgical interventions: Patient characteristics

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Otsuki et al. 2013[577]	Consecutive children who had medically refractory epilepsy with cortical dysplasia and undewent epilepsy surgery at less than 6 years of age at the National Center of Neurology and Psychiatry from December 2000 to August 2011. Patients with tuberous sclerosis, dysplastic tumors, and encephalomalacia were excluded from the study	Hemispherotomy	18	NR	15 patients (age 0); 1 patients (age 2) 2 patients (age 3)	All patients had drug-resistant multiple daily seizures, such as epileptic spasm, tonic seizures, or epilepsia partialis continua Cortical dysplasia	NR	9 infants included in this study are also reported in Iwasaki et al. 2021[1617]

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Reinholdson et al. 2015[1605]	Swedish National Epilepsy Surgery Register data capturing population based, observational cohort of children under four years of age undergoing resective epilepsy surgery in Sweden between 1995 and 2010	•Temporal lobe resection •Frontal lobe resection •Hemispherotomy	•12 •12 •12	23 male, 24 female (overall, NR for subgroup)	2 years 1 month (mean and median), range 2 months to 4 years (overall, NR for subgroup)	Hemispherotomy (7 HME, 2 polymicrogyria, 1 focal cortical dysplasia I, 1 focal cortical dysplasia unspecified, 1 gliosis/non-specific) Temporal lobe resection: 2 focal cortical dysplasia II, 3 focal cortical dysplasia unspecified, 2 gliosis/nonspecific, 4 low grade tumor, 1 tuberous sclerosis Frontal lobe resection: 2 focal cortical resection II, 5 focal cortical dysplasia unspecified, 2 gliosis or non-specific, 2 tuberous sclerosis, 1 vascular malformation	ASMs currently used: 2.2 (Mean), 2 (Median), Range 0 to 4) ASMs previously tried: 1.8 (mean), 1 (median), range (0 to 9)	None

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Kadish et al. 2019[1160]	Consecutive patients, selected from an institutional database, that 1) underwent presurgical evaluation in the cooperating Epilepsy Surgery Centers Freiburg, Heidelberg, Kork and Kiel according to the same protocol, 2) had epilepsy surgery before the age of 3 in 2001-2014 in the Epilepsy Center Freiburg, 3) were followed-up >1 year after surgery	• Intralobar resection • Multilobar resection • Hemispherotomy • Intralobar resection • Combined: hemispheric, multilobar resection	• 18 • 8 • 22 • 17 • 34	24 male	1.1 ± 0.7 year	NR	At time of surgery: mean 2 ASMs 9 (median 5) ASMs before first surgery: 27% additionally received steroids and 8% ketogenic diet	None
Steinbok et al. 2009[1606]	Patients younger than age 3 years who underwent epilepsy surgery at multiple centers across Canada from January 1987 to September 2005. Patients with surgery for a lesion, such as a tumor, who happened to present with seizures, but for whom the surgery was done for the lesion rather than the epilepsy were excluded.	• Lesionectomy • Cortical resection • Hemispheric surgery • Combined: lesionectomy, cortical resection, hemispheric	• 32 • 26 • 48 • 151	NR	Mean 15.8 months (range 1–35 months)	Detailed information on types of seizures was available for 112 children, of whom 76 presented with partial seizures, 17 with partial seizures and infantile spasm and 9 with infantile spasm only. In 41 patients there was secondary generalization of seizures. Seizure etiology only reported for all combined procedures.	NR	N for each type of surgery extrapolated from study Table 3, which represents counts for "Final seizure surgery." However, the study reported on 116 infants undergoing 152 procedures; for harms data the denominator for surgery type was unclear.

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Loddenkemper et al. 2007[483]	50 infants <3 years old among 251 consecutive pediatric patients (<18 years old) undergoing epilepsy surgery at the Cleveland Clinic between 1989 and 2001 were considered for inclusion	Combined: hemispherectomy, focal resection	24	18 male	Age of surgery: median 14 months (range: 3–34 months)	Patients presented with a median of 2 different semiological seizure types (range: 1– 4). Seizure semiology included tonic seizures (15), clonic seizures (15), epileptic spasm (11), eye versive seizures (7), hypomotor seizures (5), and myoclonic seizures (3)	At surgery, patients were taking a median of 3 ASMs (range: 0 –5)	None
Sugimoto et al. 1999[1607]	Children, aged 0-3 years, who had epilepsy surgery at The Hospital for Sick Children, Toronto, Canada, from 1991 to 1996	Focal cortical resection	10	4 male	Age of surgery: mean 18.5 months (range 8 to 34)	Seizure type at onset: Partial motor onset (unilateral) : 3 Partial motor onset: bilateral: 1 Partial motor onset, secondary generalization: 3 Complex partial seizures: 1 Partial motor seizures, changing to generalized tonic clonic seizures: 1 Partial motor seizures, changing to complex partial seizures: 1	NR	None
Dunkley et al. 2010[1608]	All children undergoing resection for epilepsy at <36 months of age and followed up for at least 2 years	• Hemispherotomy • Multilobar/lobar/focal resection	• 27 • 15	24 male, 18 female	Median 20 months (range 3 to 36)	NR	Median 3 ASMs (range 2 to 13)	None

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Kumar et al. 2015[1609]	All children under the age of 1 year undergoing surgical intervention to treat medically refractory epilepsy at Children's Hospital of Colorado between 2002 and 2013	Hemispherotomy	16	NR (by procedure)	4.5 months (Range 0.25 to 11.5)	5 focal, 4 spasm, 4 mixed, 2 tonic clonic, 1 no clinical correlate	NR	None
Iwasaki et al. 2015[1610]	Consecutive patients underwent hemispherotomy for treatment of intractable epilepsy at Tohoku University Graduate School of Medicine between 2001 and 2012	Hemispherotomy	10	7 male, 4 female	Mean 9 months (range 3 to 24)	NR	None	None
Kalbhenn et al. 2019[1611]	29 consecutive patients undergoing posterior disconnection surgery between 2005 and 2017 for the treatment of refractory posterior quadrantic epilepsy at a single center	Posterior disconnection surgery	10	NR	Mean 1.65 years (range 0.6 to 2.6)	6 Type B, 4 Type C 6 FCD, 2 ganglioma + FCD, 1 polymicrogyria, 1 meningeal angiomatosis	NR	None

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Pinto et al. 2014[1614]	Children undergoing epilepsy surgery (anatomic hemispherectomy, functional hemispherectomy, and peri-insular hemispherotomy) at Children's Hospital Boston from 1997 to 2011. Excluded patients with progressive disease including Rasmussen encephalitis and Sturge-Weber syndrome	Hemispherectomy /hemispherotomy (10 Anatomic hemispherectomy, 4 Functional hemispherectomy, 1 Peri-insular hemispherectomy)	15	NR	Mean 12.2 months (range 5 to 24)	6 focal seizures (tonic, tonic clonic or complex partial), 2 generalized tonic clonic and focal seizures, 6 infantile spasm and focal seizures, 1 infantile spasm and generalized tonic clonic seizures 8 HME, 4 Cortical dysplasia, 2 Stroke, 1 polymicrogyria	NR	None
Cook et al. 2004[293]	Children with intractable seizures undergoing hemispherectomy at UCLA's Pediatric Epilepsy Surgery Program between 1986 and 2002	Hemispherectomy/ hemispherotomy	55	NR	Mean 2.5 (SD 0.4)	53% of cortical dysplasia patients had a history of infantile spasm; no other information provided	NR	None
Jonas et al. 2004[294]	Cerebral hemispherectomy patients operated at UCLA's Pediatric Epilepsy Surgery Program from 1986 to 2002 (subset of patients included in[293])	Hemispherectomy	16	9 male, 7 female	1.5 years (SD 1.2)	9 of 16 with infantile spasm	2.5 +-0.9 ASMs	None

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Lettori et al. 2007[128]	Patients treated with hemispherectomy within 5 years of age in the Child Neurosurgery Unit of Catholic University, Rome from 1980 to December 2003, we enrolled in the study only 19 thoroughly studied children, drug resistant with at least 3 drugs at maximal dosage with no seizure control	Hemispherectomy	10	6 male, 4 female	Mean 11.3 months (range 5 to 20)	2 partial seizures only; 3 partial with partial status epilepticus ± myclonic, and tonic spasm; 3 spasm, partial seizures with or without partial status epilepticus; 1 spasm and partial, 1 tonic, partial, myoclonias	NR	None

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Roth et al. 2021[1616]	All children undergoing epilepsy surgery at <3 months or 100 days beyond 40 weeks gestation. For inclusion, infants were required to have ≥ 6 months of follow up, unless the patient died. Excluded infants with epilepsy due to hypoxic ischemic encephalopathy.	Hemispheric surgeries: 48 (25 peri-insular, 12 vertical functional hemispherectomies, 10 anatomical hemispherectomies, 1 unknown) Focal resections (7 lobectomies, 12 lesionectomy)	64	30 female, 34 male	Focal surgery: 62 days (interquartile range 43 to 86) Hemispheric surgery: 78 (interquartile range 68 to 94)	Seizure type available for 63 patients: 33 focal seizures, 6 generalized, 24 focal and generalized 28 cortical dysplasia, 17 hemimegalencephaly, 5 tubers, 4 nonspecific findings, 1 glioneuronal hamartoma, 1 stroke, 1 Sturge Weber, 1 hematoma 6 unknown	Median 4 (Interquartile range 3 to 4), range 1 to 11 ASMs prior to surgery. Continuous intravenous barbiturates or benzodiazepines (n=41) Intubated prior to surgery (n=22)	Seizure age of onset 0 to 49 days (6.6 ±11.8). 4 had suspected seizures prior to birth. 27 (42%) had experienced status epilepticus Hemispheric (including hemispherotomy, disconnection surgery) Hemispherectomy (such as anatomic hemispherectomy, regardless of surgcail technique-including combined resective/disconnective surgery) or focal (including lobar or multilobar resections_

Study	Inclusion and Exclusion Criteria	Interventions	n	Gender	Age at Intervention	Seizure Etiology and Type	Prior Treatments	Comments
Iwasaki et al. 2021[1617]	Infants undergoing "first curative epilepsy surgery" at <3 between August 2006 and February 2019 at the National Center of Neurology and Psychiatry, Tokyo, Japan For inclusion, patients were required to have ≥ 1 year follow up post operative, and post-operative developmental assessment at 1 year or the last follow up after 2 years or longer. Excluded patients who had undergoing palliative procedures (corpus callosomty and vagus nerve stimulation implantation).	Hemispherotomy (22 vertical parasaggital hemispherotomies, 5 periinsular hemispherotomies) 19 multilobar surgeries (1 subtotal hemispherotomy, 13 posterior quadrantic disconnections, 5 multilobar cortical resections) 29 unilobar surgieres (8 anterior temporal lobectomies, 5 frontal lobectomies or disconnections, 16 focal cortical resections or lesionectomies)	75	39 female, 36 male	For all surgeries mean age 11.9 ± 10.8 months, median 6 months, range 58 days to 35 months) NR separately by procedure type	Etiology was hemimegalencephaly (HME) 22, other malformations of cortical development 33, low-grade developmental tumors 10, tuberous sclerosis complex 6, Surge-Weber syndrome 3, perinatal ischemia 1. Type of seizures NR	ASMs at surgery mean 2.21 (range 1-6)	Authors report 81 infants underwent surgery at <3; only 6 patients were excluded for <1 year of follow up or no postoperative developmental assessments available Note: 15 of 75 infants were diagnosed with West syndrome Presurgical seizure frequency:68 infants had daily seizures, 6 had weekly seizures; "one patients with Sturge-Weber syndrome presented with rare clinical seizures before surgery"

NA = not applicable; NR = not reported; NRFS = not reported for the subgroup; IQR = interquartile range; ASM = antiseizure medication

Table C-32. Harms of surgical interventions: Treatment characteristics

Study	Intervention	n	Treatment Details	Seizure Measurement Methods	Comments
Otsuki et al. 2013[577]	Hemispherotomy	18	NR	ILAE classification	9 infants included in this study are also reported in Iwasaki et al. 2021[1617]
Reinholdson et al. 2015[1605]	•Temporal lobe resection •Frontal lobe resection •Hemispherotomy	•12 •12 •12	NR	Seizure frequency	None
Kadish et al. 2019[1160]	•Intralobar resection •Multilobar resection •Hemispherotomy •Intralobar resection •Combined: hemispheric, multilobar resection	•18 •8 •22 •17 •34	NR	Seizure freedom Engel classification	None
Steinbok et al. 2009[1606]	•Lesionectomy •Cortical resection •Hemispheric •Combined: lesionectomy, cortical resection, hemispheric	•32 •26 •48 •151	NR	Engel classification	None
Loddenkemper et al. 2007[483]	Combined: hemispherectomy, focal resection	24	Surgeries (13 right, 11 left) included 14 hemispherectomies and 10 focal resections (3 frontal, 3 frontoparietal, 2 parietal, 1 parieto-occipital, and 1 occipital).	Seizure frequency Seizure freedom	None
Sugimoto et al. 1999[1607]	Focal cortical resection	10	NR	Engel classification	None
Dunkley et al. 2010[1608]	•Hemispherotomy •Multilobar/lobar/focal resection	• 27 • 15	NR	NR	None
Kumar et al. 2015[1609]	Hemispherotomy	16	NR	Engel classification	None

Study	Intervention	n	Treatment Details	Seizure Measurement Methods	Comments
Iwasaki et al. 2015[1610]	Hemispherotomy	10	3 periinsular hemispherotomies, 7 vertical hemispherotomies	Engel classification	None
Kalbhenn et al. 2019[1611]	Posterior disconnection surgery	10	NR	Seizure freedom	None
Pinto et al. 2014[1614]	Hemispherectomy /hemispherotomy	15	10 Anatomic hemispherectomy, 4 Functional hemispherectomy, 1 Peri-insular hemispherectomy	Engel classification	None
Cook et al. 2004[293]	Hemispherectomy/ hemispherotomy	55	Of 55 patients, 14 anatomic hemipherectomies, 15 functional hemispherectomies, and 26 hemispherotomy	Seizure freedom	None
Jonas et al. 2004[294]	Hemispherectomy	16	NR	Seizure freedom	None
Lettori et al. 2007[128]	Hemispherectomy	10	6 Anatomical; 2 Functional; 1 functional + hemidecortication; 1 hemidecortication	Engel classification	None
Roth et al. 2021[1616]	• Hemispherectomy/Hemispherotomy • Focal resection	• 48 • 19	25 periinsular, 12 vertical functional hemispherotomies, 10 anatomic hemispherectomy 12 focal resections, 7 lobectomies	Engel classification	None

Study	Intervention	n	Treatment Details	Seizure Measurement Methods	Comments
Iwasaki et al. 2021[1617]	• Hemispherotomies • Multilobar surgeries • Unilobar surgeries	• 27 • 19 • 29	22 vertical parasagittal hemispherotomy, 5 periinsular hemispherotomy 1 subtotal hemispherotomy, 13 posterior quadrantic disconnection, 5 multilobar cortical resections 8 anterior temporal lobectomies, 5 frontal lobectomies or disconnections, 16 focal cortical resection or lesionectomies	ILAE classification (but NR by procedure type)	Note: 9 infants included in this study were already included in another study (Otsuki et al. 2013[577]) included in this systemtic review. Also, 15 of 75 (20%) of included infants were diagnosed with West syndrome

NA = not applicable; NR = not reported; NRFS = not reported for the subgroup

Table C-33. Harms: Mortality for all surgical procedures

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Cook et al. 2004[293]	Anatomical hemispherectomy	Mortality	NR	1/14	Study reports “one death occurred intraoperatively in an 8 month old child with hemimegalencephaly” under “Surgical Related Compllications” and in Table 6.
Dunkley et al. 2010[1608]	Anatomic Hemispherectomy	Mortality	NR	0/2	Table 4 describes “Surgical complications, reoperations rates and mortality” and reports no deaths.

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Roth et al. 2021[1616]	Anatomic Hemispherectomy	Mortality	"Perioperative"	0/10	Section 3.4 reports, "There were no peri-operative deaths." Authors reported that for 1 patient, the type of hemispheric surgery was unknown. As we categorized mortality by anatomic vs. functional hemispherectomyohemispherotomy, we did not include this patient. Thus, for mortality, the total number of hemispheric procedures included in the report totals to 47 of 48 included in the study.
Cook et al. 2004[293]	Functional hemispherectomy/Hemispherotomy	Mortality	NR	0/41	None
Dunkley et al. 2010[1608]	Functional Hemispherectomy	Mortality	NR	0/25	Table 4 describes "Surgical complications, reoperations rates and mortality" and reports no deaths.
Iwasaki et al. 2015[1610]	Hemispherotomy	Mortality	NR	0/10	No specific timepoint for this outcome was reported. "No morbidity or mortality was related to the surgical procedures in the present case series…"
Kadish et al. 2019[1160]	Hemispherotomy	Mortality	NR	0/22	No specific timepoint reported: "there were not perioperative mortalities"
Kumar et al. 2015[1609]	Hemispherotomy	Mortality	"Perioperative"	1/16	Infant with epidermal nevus syndrome, right hemimegalencephaly, and multiple other congential abnormalities. Pre-operative EEG showed majority of seizures originating from hemimegalic side; post-operatively, he developed refractory seizures from contralateral hemisphere and care was withdrawn.
Otsuki et al. 2013[577]	Hemispherotomy	Mortality	NR	0% (0/18)	Study describes "Surgical mortality" and states "No mortality or severe morbidity occurred" 9 infants included in this study are also reported in Iwasaki et al. 2021[1617]

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Roth et al. 2021[1616]	Peri-insular and vertical functional hemispherotomies	Mortality	"Perioperative"	0/37	Section 3.4 reports, "There were no peri-operative deaths." Authors reported that for 1 patient, the type of hemispheric surgery was unknown. As we categorized mortality by anatomic vs. functional hemispherectomyohemispherotomy, we did not include this patient. Thus, for mortality, the total number of hemispheric procedures included in the report totals to 47 of 48 included in the study. For mortality, 7 patients from 3 of 19 centers may also have been described in prior studies.[293,483,1608]
Iwasaki et al. 2021[1617]	Hemispherotomy (periinsular hemispherotomy, vertical parasaggital hemispherotomy)	Mortality	≥ 1 year after surgery (or longer)	0/27	Study included 20% infants with West syndrome; also 9 of 75 infants were also included in a prior study (Otsuki et al. 2013[577]) that was also included in this report.
Iwasaki et al. 2021[1617]	Multilobar surgery, Unilobar surgery	Mortality	≥ 1 year after surgery (or longer)	0/48	0/19 Multilobar surgery, 0/29 unilobar surgery Study included 20% infants with West syndrome; also 9 of 75 infants were also included in a prior study (Otsuki et al. 2013[577]) that was also included in this report.
Dunkley et al. 2010[1608]	Multilobar/Lobar/Focal Resection	Mortality	NR	0/15	Table 4 describes "Surgical complications, reoperations rates and mortality" and reports no deaths.
Roth et al. 2021[1616]	Focal resections, lobectomies	Mortality	"Perioperative"	0/19 procedures	0/12 focal resections, 0/7 lobectomies For mortality, 7 patients from 3 of 19 centers may also have been described in prior studies.[293,483,1608]

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Steinbok et al. 2009[1606]	Lesionectomy, cortical resection, and hemispheric surgery	Mortality	≥ 1 year after surgery (or longer)	1 death (in 116 patients undergoing 151 procedures)	1 intraoperative death (3.9 month child with tuberous sclerosis who underwent attempted resection of intraventricular and extraventricular lesions); unclear what type of surgical procedure

Table C-34. Adverse events (hemispherectomy/hemispherotomy)

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Cook et al. 2004[293]	Anatomical hemispherectomy (n=14)	CNS infection	NR	2/14	None
Cook et al. 2004[293]	Anatomical hemispherectomy (n=14)	Blood clot requiring reoperation	NR	1/14	None
Cook et al. 2004[293]	Anatomical hemispherectomy (n=14)	Cranial nerve III palsy	NR	1/14	None
Cook et al. 2004[293]	Anatomical hemispherectomy (n=14)	Inappropriate antidiuretic hormone	NR	1/14	None
Dunkley et al. 2010[1608]	Anatomic Hemispherectomy	Ventriculoperitoneal (VP) shunt	Shunts placed 12 months after surgery	2/2	None
Lettori et al. 2007[128]	Anatomical hemispherectomy (n=6), Hemidecortication (n=1)	Hydrocephalus	NR	3/7	None
Lettori et al. 2007[128]	Anatomical hemispherectomy (n=6), Hemidecortication (n=1)	Infection (1 Superficial, 1 Deep)	NR	2/7	None
Lettori et al. 2007[128]	Anatomical hemispherectomy (n=6), Hemidecortication (n=1)	Subdural fluid collection	NR	1/7	None
Lettori et al. 2007[128]	Anatomical hemispherectomy (n=6), Hemidecortication (n=1)	Cerebrospinal Fluid Leakage	NR	1/7	None
Lettori et al. 2007[128]	Anatomical hemispherectomy (n=6), Hemidecortication (n=1)	Transient fever	NR	2/7	None
Pinto et al. 2014[1614]	Anatomic hemispherectomy (n=10)	VP shunt	NR	7/10	None

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Cook et al. 2004[293]	Functional hemispherectomy/Hemispherotomy (n=41)	CNS infection	NR	2/41	None
Cook et al. 2004[293]	Functional hemispherectomy/Hemispherotomy (n=41)	Dural adhesions requiring "late reoperation"	NR	1/41	None
Dunkley et al. 2010[1608]	Functional Hemispherectomy	Ventriculoperitoneal (VP) shunt (n=2)/ Lumboperitoneal (VP) shunt (n=1)	6 weeks, 6 months, 4 years respectively	3/27	None
Iwasaki et al. 2015[1610]	Hemispherotomy	VP shunt placement	NR	0/10	" No morbidity or mortality was related to the surgical procedures in the present case series…" "No patients required cerebrospinal fluid shunt operation for hydrocephalus"
Iwasaki et al. 2021[1617]	Hemispherotomy (periinsular hemispherotomy, vertical parasaggital hemispherotomy)	Hydrocephalus requiring surgical intervention	NR	6/27	Of 6 cases, 5 underwent vertical parasaggital hemispherotomy and 1 underwent periinsular hemispherotomy) (see Table 1) However, authors report performing CSF diversion on for other conditions as well: "Cystic enlargement of the postoperative cavity or hydrocephalus with or without subdural fluid collection occurred in 13 patients (17.3%). All of these patients were treated with CSF diversion surgery, including ventriculoperitoneal shunt placement in 6 patients, cyst-peritoneal shunt insertion in 3, subdural-peritoneal shunt placement in 2, and cyst fenestration in 2. The symptom was often subacute, and the median interval between epilepsy surgery

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
					and CSF diversion was 4 months (range 26 days–30 months)."
Iwasaki et al. 2021[1617]	Hemispherotomy (periinsular hemispherotomy, vertical parasaggital hemispherotomy)	Cyst formation requiring surgical intervention	NR	2/27	2 infants undergoing vertical parasaggital hemispherotomy (see Table 1) Study outcomes were reported at minimum 12 months after surgery
Iwasaki et al. 2021[1617]	Hemispherotomy (periinsular hemispherotomy, vertical parasaggital hemispherotomy)	Cerebral salt wasting syndrome	NR	2/27	2 infants undergoing vertical parasaggital hemispherotomy (see Table 1) Study outcomes were reported at minimum 12 months after surgery
Iwasaki et al. 2021[1617]	Hemispherotomy (periinsular hemispherotomy, vertical parasaggital hemispherotomy)	Diabetes insipidus	NR	3/27	3 infants undergoing vertical parasaggital hemispherotomy (see Table 1) Study outcomes were reported at minimum 12 months after surgery
Iwasaki et al. 2021[1617]	Hemispherotomy (periinsular hemispherotomy, vertical parasaggital hemispherotomy)	Sinus thrombosis (attributed to diabetes insipidus by study authors)	NR	2/27	2 infants undergoing vertical parasaggital hemispherotomy (see Table 1) Study outcomes were reported at minimum 12 months after surgery
Iwasaki et al. 2021[1617]	Hemispherotomy (periinsular hemispherotomy, vertical parasaggital hemispherotomy)	Asymptomatic hemorrhagic infarction	NR	1/27	1 infants undergoing vertical parasaggital hemispherotomy (see Table 1) Study outcomes were reported at minimum 12 months after surgery
Kadish et al. 2019[1160]	Hemispherotomy	VP shunt placement	NR	16%	"16% of hemispherotomy patients developed hydrocephalus that required VP shunt placement."
Kadish et al. 2019[1160]	Hemispherotomy	Acute post surgical seizures	NR	23%	None

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Kadish et al. 2019[1160]	Hemispherotomy	Epidural hemorrhage requiring surgical revision	"Early post surgical course"	1/22	"Epidural hemorrhage requiring surgical revision occurred in the early postsurgical course of a hemimegalencephaly patient with a coagulation disorder who underwent hemispherotomy at 8 mo of age."
Kadish et al. 2019[1160]	Hemispherotomy	Pituitary failure (due to thalamic lesion"	NR	1/22	Unclear if denominator is all hemispherotomies; 22 is number of initial hemispherotomies
Kumar et al. 2015[1609]	Hemispherotomy	Hydrocephalus	NR specifically for hydrocephalus; however, study follow up was a mean 56 months (range 3 to 133)	4/16	Surgical complications were recorded in the acute post-operative setting as well as during subsequent clinic visits.
Kumar et al. 2015[1609]	Hemispherotomy	Inadvertent extubation	NR specifically for hydrocephalus; Mean 56 months (range 3 to 133) however, study follow up was a mean 56 months (range 3 to 133)	1/16	Surgical complications were recorded in the acute post-operative setting as well as during subsequent clinic visits
Kumar et al. 2015[1609]	Hemispherotomy	Excessive bleeding	NR specifically for hydrocephalus; however, study follow up was a mean 56 months (range 3 to 133)	1/16	Surgical complications were recorded in the acute post-operative setting as well as during subsequent clinic visits
Lettori et al. 2007[128]	2 Functional hemispherectomy; 1 functional + hemidecortication	Hydrocephalus	NR	1/3	None
Lettori et al. 2007[128]	2 Functional hemispherectomy; 1 functional + hemidecortication	Infection (Superficial)	NR	1/3	None

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
Pinto et al. 2014[1614]	4 Functional hemispherectomy, 1 Peri-insular hemispherectomy	VP shunt	NR	1/5	Study reports seizure outcomes measured at minimum of 12 months after surgery; however, timepoint for shunt placement not explicitly reported
Reinholdson et al. 2015[1605]	Hemispherectomy	VP shunt	Within 2 years	1/12	1 child required ventriculoperitoneal shunt within 2 years after hemispherotomy
Roth et al. 2021[1616]	25 periinsular, 12 vertical functional hemispherotomies, 10 anatomic hemispherectomies	Hydrocephalus	NR specifically for hydrocephalus; however, follow up for hemispheric surgeries was median 51 months (IQR 27 to 126)	11/44	"Type of surgery was significantly correlated with postoperative hydrocephalus (25% of hemispheric surgery vs. 0% of focal surgeries, p=0.025)" Outcome reported for 44 patients (author correspondence). For hydrocephalus, 1 patients may also have been described in a prior study. [1608]
Steinbok et al. 2009[1606]	Hemispherectomy/Hemispherotomy 40 (1 anatomical, 6 hemidecortication, 22 functional hemispherectomies, 12 peri-insular hemispherotomies)	Blood transfusion	During operation	31/40	Other harms were reported, but not by specific procedure except for blood transfusion for which only counts from first procedure were reported. For instance adverse events combined across multiple procedures (including hemispherectomies, but also focal cortical resections, lesionectomies, and lobectomies) included cerebral infarct, epidural hematoma, deep venous thrombosis, septicemia, pneumonia, wound infection, and pseudomeningocele (see Table 2)
Steinbok et al. 2009[1606]	Hemispherectomy/Hemispherotomy	Aseptic meningitis	Peri-operative	13 (unclear denominator)	Study does not specify which hemispheric procedures were involved.

Study	Intervention	Harm	Timepoint	Rate (Events/N)	Comments
					"Thirteen surgeries, all hemispheric procedures, were complicated by aseptic meningitis, which was managed successfully with steroids."
Steinbok et al. 2009[1606]	Hemispherectomy/Hemispherotomy	Hydrocephalus	Within a "few months" after surgery	4 (unclear denominator)	Study does not specify a denominator. "Seven children.. four with functional hemispherectomy and three with cortical resections, developed hydrocephalus after surgery—one child immediately postsurgery due to hemorrhage, one after the third operation, and the remainder within a few months after surgery."

Table C-35. Adverse events (non-hemispheric procedures)

Study	Intervention	Harms	Timepoint	Rate (Events/N)	Comments
Dunkley et al. 2010[1608]	Multilobar/Lobar/Focal Resection	VP shunt placement	NR	0/15	None
Iwasaki et al. 2021[1617]	Multilobar Surgery, Unilobar surgery	Hydrocephalus requiring surgical intervention	NR	0/48	Timepoint for this outcome NR, but study outcomes were reported at minimum 12 months after surgery
Iwasaki et al. 2021[1617]	Multilobar Surgery, Unilobar surgery	Asymptomatic cerebral infarction (requiring medical treatment)	NR	1/48	Occurred in 1/13 infants undergoing posterior quadrantic disconnection (see Table 1) Timepoint for this outcome NR, but study outcomes were reported at minimum 12 months after surgery

Study	Intervention	Harms	Timepoint	Rate (Events/N)	Comments
Iwasaki et al. 2021[1617]	Multilobar Surgery, Unilobar surgery	Cyst formation requiring surgical intervention	NR	2/48	Occurred in infants undergoing posterior quadrantic disconnection (n=1), multilobar cortical resection (n=1) (see Table 1) Timepoint for this outcome NR, but study outcomes were reported at minimum 12 months after surgery
Iwasaki et al. 2021[1617]	Multilobar Surgery, Unilobar surgery	Subdural hygroma requiring surgical intervention	NR	3/48	Occurred in infants undergoing multibloar cortical resection (n=1), frontal lobectomy or disconnection (n=1), and forcal cortical resection or lesionectomy (n=1) (see Table 1) Timepoint for this outcome NR, but study outcomes were reported at minimum 12 months after surgery
Iwasaki et al. 2021[1617]	Multilobar Surgery, Unilobar surgery	Infection (bacterial meningitis)	NR	1/48	Occurred in 1 infant underoing frontal lobectomy or disconnection (see Table 1) Timepoint for this outcome NR, but study outcomes were reported at minimum 12 months after surgery

Study	Intervention	Harms	Timepoint	Rate (Events/N)	Comments
Iwasaki et al. 2021[1617]	Multilobar Surgery, Unilobar surgery	Psychiatric symptom	NR	1/48	Occurred in 1 infant underoing anterior temporal lobectomy (see Table 1) Timepoint for this outcome NR, but study outcomes were reported at minimum 12 months after surgery
Kadish et al. 2019[1160]	Intralobar/Multilobar resection	VP shunt placement	NR	0/26	None
Kalbhenn et al. 2019[1611]	Posterior Disconnection	Transient hemiparesis	24 months after surgery	1/10	None
Roth et al. 2021[1616]	Focal resections, Lobectomies	Hydrocephalus	NR specifically for hydrocephalus; however, follow up for focal surgeries was median 24 months (IQR 5 to 55)	0/19	12 focal resections, 7 lobectomies Author correspondence confirmed this outcome reported for 19 infants. For hydrocephalus, 1 patients may also have been described in a prior study.[1608]

Study	Intervention	Harms	Timepoint	Rate (Events/N)	Comments
Steinbok et al. 2009[1606]	Cortical Resections	Hydrocephalus	Within a "few months" after surgery	3 (unclear denominator)	Study does not specify a denominator. "Seven children.. four with functional hemispherectomy and three with cortical resections, developed hydrocephalus after surgery—one child immediately postsurgery due to hemorrhage, one after the third operation, and the remainder within a few months after surgery."

NR = not reported

Table C-36. Harms of surgical interventions: Harms outcomes

Study	Intervention	Adverse Event	Hospitalization, Mortality, SUDEP	Comments
Otsuki et al. 2013[577]	Hemispherotomy	Perioperative complication: No patient had a history of perinatal or postnatal systemic complications suggesting brain injury.	No mortality or severe morbidity	9 infants included in this study are also reported in Iwasaki et al. 2021[1617]
Reinholdson et al. 2015[1605]	•Temporal lobe resection •Frontal lobe resection •Hemispherotomy	Post-operative complication: 4 children with hemispherotomy went on to have completion of hemispherotomy 1 child required ventriculoperitoneal shunt within 2 years after hemispherotomy	NR	None

Study	Intervention	Adverse Event	Hospitalization, Mortality, SUDEP	Comments
Kadish et al. 2019[1160]	• Intralobar resection • Multilobar resection • Hemispherotomy • Intralobar resection • Combined: hemispheric, multilobar resection	Epidural hemorrhage requiring surgical revision occurred in the early postsurgical course of a hemimegalencephaly patient with a coagulation disorder who underwent hemispherotomy at 8 months of age. 16% of hemispherotomy patients developed hydrocephalus that required ventriculoperitoneal shunt placement; 1 child had pituitary failure due to a thalamic lesion. There were no perioperative mortalities. Acute postsurgical seizures occurred in 23% of cases.	NR	None
Steinbok et al. 2009[1606]	• Lesionectomy • Cortical resection • Hemispheric • Combined: lesionectomy, cortical resection, hemispheric	**Hemispheric**: 4 hydrocephalus; 13 aseptic meningitis (managed successfully with steroids) **Cortical Resection**: 3 hydrocephalus **Combined:** Infection: 17 Aseptic meningitis: 13 Hydrocephalus: 7 Cerebral infarct: 4 Transient mutism: 2 Pseudomeningocele: 2 Syndrome of inappropriate ADH secretion: 4 Subdural hematoma: 2 Epidural hematoma: 1 Deep venous thrombosis: 1 Severe intravenous infiltration in the arm: 1	1 intraoperative death (3.9 month child with tuberous sclerosis who underwent attempted resection of intraventricular and extraventricular lesions); unclear what type of surgical procedure.	Authors report: "Seven children …four with functional hemispherectomy and three with cortical resections, developed hydrocephalus after surgery—one child immediately postsurgery due to hemorrhage, one after the third operation, and the remainder within a few months after surgery."
Loddenkemper et al. 2007[483]	Combined: hemispherectomy, focal resection	NR	NR	None
Sugimoto et al. 1999[1607]	Focal cortical resection	NR	NR	No details provided on how delay is measured.

Study	Intervention	Adverse Event	Hospitalization, Mortality, SUDEP	Comments
Dunkley et al. 2010[1608]	•Hemispherotomy •Multilobar/lobar/focal resection	**Hemispherotomy:** Complications: • 4 ventriculoperitoneal (VP) shunts • 1 lumboperitoneal shunt Reoperation: • 2 further disconnections • 1 extension to anatomical hemipherectomy **Multilobar/lobar/focal resection:** Complication: 0 Reoperation: 1 (1 lobar (extended to multilobar); 3 focal (extended to lobar or multilobar)	•Mortality: 0 •Mortality: 0	None
Kumar et al. 2015[1609]	Hemispherotomy	Complications: Hydrocephalus: 4 Excessive bleeding: 1 Inadvervent extubation: 1	Mortality: 1 Infant with epidermal nevus syndrome, right hemimegalencephaly, and multiple other congential abnormalities. Pre-operative EEG showed majority of seizures originating from hemimegalic side; post-operatively, he developed refractory seizures from contralateral hemisphere and care was withdrawn.	None
Iwasaki et al. 2015[1610]	Hemispherotomy	No complication recorded	Mortality: 0	None
Kalbhenn et al. 2019[1611]	Posterior disconnection surgery	Transient hemiparesis: 1	NR	None

Study	Intervention	Adverse Event	Hospitalization, Mortality, SUDEP	Comments
Pinto et al. 2014[1614]	Anatomic hemispherectomy, Functional hemispherectomy, Peri-insular hemispherectomy	VP Shunt: 8	NR	None
Cook et al. 2004[293]	Hemispherectomy/ hemispherotomy	Central nervous system infection: 4 • Anatomical: 2 • Functional: 1 • Hemispherotomy: 1 Reoperation for recurrent seizures: 10 •Functional Hemispherectomy: 6 •Hemispherotomy: 4 Inappropriate Antidiuretic hormone: 1 (Anatomical hemispherectomy) Cranial nerve III palsy: 1 (Anatomical Hemispherectomy) Reoperation blood clot: 1 (Anatomical hemispherotomy) Late reoperation for dural adhesions: 1 (Functional hemispherectomy)	1 mortality (anatomical hemispherectomy)	None
Lettori et al. 2007[128]	Hemispherectomy	Hydrocephalus: 3 Infection: 3 Transient fever: 2 Subdural fluid collection: 1 CSF leakage: 1	NR	None

Study	Intervention	Adverse Event	Hospitalization, Mortality, SUDEP	Comments
Roth et al. 2021[1616]	Hemispherectomy/Hemispherotomy Focal resection/lobectomy	Hydrocephalus: Hemispherectomy/hemispherotomy 12 of 48; Focal resection 0 of 12 Disseminated intravascular coagulation: 1 (hemispherotomy), resulting in procedure being aborted **Combined incidence for intraoperative complications for hemispherectomy/hemispherotomies/focal resections**: Hypotension: 7 Hypothermia: 4 "respiratory related complications": 5 Transfusion related reaction: 1 Injury to superior sagittal sinus: 1 Vocal cord injury: 1 Difficult intubation: 1 Retained cottonoid: 1 **Post-operative complications (combined)** Additional blood products needed: 16 Respiratory complications: 7 Infections (meningitis/abscess): 4 Wound complications: 7	Mortality: 0	"Preoperative EEG activity was correlated with more intraoperative systemic complications, more need for intra- and postoperative blood products, and more post operative hydrocephalus." This correlation was not explained by type of surgery (hemispheric vs. focal) except for hydrocephalus.

Study	Intervention	Adverse Event	Hospitalization, Mortality, SUDEP	Comments
Iwasaki et al. 2021[1617]	Hemispherotomies Multilobar surgeries Unilobar surgeries	**Post-operative complications requiring surgical intervention** Hydrocephalus: 6 hemispherotomies Cyst formation: 2 hemispherotomies, 1 multilobar resection Subdural hygroma: 1 multilobar surgery, 2 unilobar surgeries **Post-operative complications requiring medical treatment** Cerebal salt wasting syndrome: 2 hemispherotomies Diabetes insipidus: 2 hemispherotomies Sinus thrombosis (after diabetes insipidus): 2 hemispherotomies Asymptomatic hemorrhagic infarction:1 hemispherotomy Asymptomatic cerebral infarction: 1 multilobar surgery (posterior quadrantic disconnection) Psychiatric symptom: 1 unilobar surgery (anterior temporal lobectomy) Bacterial meningitis: 1 unilobar surgery (frontal lobectomy or disconnection)	Mortality: 0	Harms data appears in study Table 1. Note: 9 infants included in this study were already included in another study (Otsuki et al. 2013[577]) included in this systemtic review. Also, 15 of 75 (20%) of included infants were diagnosed with West syndrome

NA = not applicable; NR = not reported; NRFS = not reported for the subgroup

Table C-37. Risk of bias: Surgical mortality for surgical procedures

Study	Surgery	Study Addressed Ootential Confoundingt	Fidelity To Intervention Protocol	Bias Due To Attrition	Outcome Assessor Blinding*	Intervention Or Exposure Defined Using Valid/reliable Measures**	Outcomes Assessed Using Calid/reliable Measures And Implemented Consistently	Confounding Variables Assessed Using Valid/reliable Measures Across All Participants	Outcomes Prespecified And Reported*	Overall Risk Of Bias
Cook et al. 2004[293]	Anatomic Hemispherectomy	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low
Dunkley et al. 2010[1608]	Anatomic Hemispherectomy	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low
Roth et al. 2021[1616]	Anatomic Hemispherectomy	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low

Study	Surgery	Study Addressed Ootential Confounding†	Fidelity To Intervention Protocol	Bias Due To Attrition	Outcome Assessor Blinding*	Intervention Or Exposure Defined Using Valid/reliable Measures**	Outcomes Assessed Using Calid/reliable Measures And Implemented Consistently	Confounding Variables Assessed Using Valid/reliable Measures Across All Participants	Outcomes Prespecified And Reported*	Overall Risk Of Bias
Cook et al. 2004[293]	Functional hemispherectomy or Hemispherotomy	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low
Dunkley et al. 2010[1608]	Functional hemispherectomy	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low
Iwasaki et al. 2015[1610]	Interhemispheric vertical hemispherorotomy	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low
Kadish et al. 2019[1160]	Hemispherectomy	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low
Kumar et al. 2015[1609]	Hemispherotomy	Low	Low	Low	Low	Low	Low	Low	Low	Low
Otsuki et al. 2013[577]	Hemispherotomy	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low
Iwasaki et al. 2021[1617]	Hemispherotomy/ Multilobar/Unilobar resection	Low	Low	Low	Low	Low	Low	Low	Low	Low
Roth et al. 2021[1616]	Hemispherectomy/ Hemispherotomy or Focal Resection	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low
Dunkley et al. 2010[1608]	Mutilobar or Lobar resection	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low

† Factors considered included whether studies reported seizure etiology, baseline seizure rate, or concurrent therapies such as number of antiseizure medications (ASM) or specific ASM used.

*As all studies used a retrospective pre/post design, no outcome assessors were blinded and no outcomes were prespecified except for Reinholdson, which utilized prospectively collected registry data. However, we judged seizure freedom (and mortality) to not be affected by lack of blinding or prespecification of outcomes, so these were rated low risk of bias.

** All studies described the type of surgical procedure, so we rated this low risk of bias for all studies.

Overall risk of bias for all studies was rated High, as no studies had a control group.

Table C-38. Risk of bias: Hydrocephalus after multilobar, unilobar, or focal resection

Study	Surgery	Study Addressed Ootential Confounding†	Fidelity To Intervention Protocol	Bias Due To Attrition	Outcome Assessor Blinding*	Intervention Or Exposure Defined Using Valid/reliable Measures**	Outcomes Assessed Using Calid/reliable Measures And Implemented Consistently	Confounding Variables Assessed Using Valid/reliable Measures Across All Participants	Outcomes Prespecified And Reported*	Overall Risk Of Bias
Dunkley et al. 2010[1608]	Multilobar or Lobar Resection	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low
Iwasaki et al. 2021[1617]	Multilobar or Unilobar Resection	Low	Low	Low	Low	Low	Low	Low	Low	Low
Kadish et al. 2019[1160]	Multilobar/Intralobar Resection	Low	Low	Low	Low	Low	Low	Low	Low	Low
Roth et al. 2021[1616]	Focal Resections lesionectomies and lobectomies)	Low	Low	Low	Low	Low	Low	Low	Low	Low
Steinbok et al. 2009[1606]	Cortical Resections	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low

† Factors considered included whether studies reported seizure etiology, baseline seizure rate, or concurrent therapies such as number of antiseizure medications (ASM) or specific ASM used.

*As all of these studies used a retrospective pre/post design, no outcome assessors were blinded and no outcomes were prespecified. However, we judged hydrocephalus (reported as requiring surgical intervention in 4 of 5 studies to not be affected by lack of blinding or prespecification of outcomes, so these were rated low risk of bias).

** All studies described the type of surgical procedure, so we rated this low risk of bias for all studies.

Appendix D. Appendix References

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Appendix E. PCORI Methodology Standards Checklist: Systematic Review

PCORI Methodology Standards Checklist: Systematic Review (SR)					
Contract No.	AHRQ 75Q80120D00002				
Task Order No.	AHRQ 75Q80120F32004				
EPC	ECRI-Penn				
Project Title	Management of Infantile Epilepsies				
Standard Category	**Abbrev.**	**Standard**	**Is this standard applicable to this SR?**	**List sections and pages of the SR report where you address this standard**	**If applicable, describe how and why the SR deviated from this standard?**
Cross-Cutting Standards for PCOR					
Standards for Formulating Research Questions	RQ-1	Identify gaps in evidence.	Yes	2	
	RQ-2	Develop a formal study protocol.	Yes	4	
	RQ-3	Identify specific populations and health decision(s) affected by the research.	Yes	1 to 3	
	RQ-4	Identify and assess participant subgroups.	Yes	6	
	RQ-5	Select appropriate interventions and comparators.	Yes	4 to 6	

	RQ-6	Measure outcomes that people representing the population of interest notice and care about.	Yes	6	
Standards Associated with Patient-Centeredness	PC-1	Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context.	Yes	4	
	PC-2	Identify, select, recruit, and retain study participants representative of the spectrum of the population of interest and ensure that data are collected thoroughly and systematically from all study participants.	No	NA	
	PC-3	Use patient-reported outcomes when patients or people at risk of a condition are the best source of information for outcomes of interest.	No	NA	

	PC-4	Support dissemination and implementation of study results.	Yes	8	
Standards for Data Integrity and Rigorous Analyses	IR-1	A priori, specify plans for quantitative data analysis that correspond to major aims.	No	NA	
	IR-2	Assess data source adequacy.	Yes	7	
	IR-3	Describe data linkage plans, if applicable.	No	NA	
	IR-4	Document validated scales and tests.	No	NA	
	IR-5	Provide sufficient information in reports to allow for assessments of the study's internal and external validity.	Yes	Appendix C	
	IR-6	Masking should be used when feasible.	No	NA	
	IR-7	In the study protocol, specify a data management plan that addresses, at a minimum, the following elements: collecting data, organizing data,	Yes	7	

		handling data, describing data, preserving data, and sharing data.			
Standards for Preventing and Handling Missing Data	MD-1	Describe methods to prevent and monitor missing data.	No	NA	
	MD-2	Use valid statistical methods to deal with missing data that properly account for statistical uncertainty due to missingness.	No	NA	
	MD-3	Record and report all reasons for dropout and missing data, and account for all patients in reports.	No	NA	
	MD-4	Examine sensitivity of inferences to missing data methods and assumptions, and incorporate into interpretation.	No	NA	
Standards for Heterogeneity of Treatment Effect (HTE)	HT-1	State the goals of HTE analyses, including hypotheses and the supporting evidence base.	No	NA	

	HT-2	For all HTE analyses, provide an analysis plan, including the use of appropriate statistical methods.	No	NA	
	HT-3	Report all prespecified HTE analyses and, at minimum, the number of post-hoc HTE analyses, including all subgroups and outcomes analyzed.	No	NA	
Standards for Specific Study Designs and Methods					
Standards for Data Registries	DR-1	Requirements for the design of registries.	No	NA	
	DR-2	Documentation and reporting requirements of registry materials, characteristics, and bias.	No	NA	
	DR-3	Adapting established registries for PCOR.	No	NA	
	DR-4	Documentation requirements when using registry data.	No	NA	
Standards for Data Networks as Research-	DN-1	Requirements for the design and features of data networks.	No	NA	

Facilitating Structures	DN-2	Selection and use of data networks.	No	NA	
Causal Inference Standards	CI-1	Specify the causal model underlying the research question (cross-cutting standard, applies to all PCOR/CER studies).	No	NA	
	CI-2	Define and appropriately characterize the analysis population used to generate effect estimates.	No	NA	
	CI-3	Define with the appropriate precision the timing of the outcome assessment relative to the initiation and duration of exposure.	No	NA	
	CI-4	Measure potential confounders before start of exposure and report data on potential confounders with study results.	No	NA	
	CI-5	Report the assumptions underlying the construction of propensity	No	NA	

		scores and the comparability of the resulting groups in terms of the balance of covariates and overlap.			
	CI-6	Assess the validity of the instrumental variable (i.e., how the assumptions are met) and report the balance of covariates in the groups created by the instrumental variable.	No	NA	
Standards for Adaptive and Bayesian Trial Designs	AT-1	Specify planned adaptations, decisional thresholds, and statistical properties of those adaptations.	No	NA	
	AT-2	Specify the structure and analysis plan for Bayesian adaptive randomized clinical trial designs.	No	NA	
	AT-3	Ensure that clinical trial infrastructure is adequate to support planned adaptation(s) and independent	No	NA	

		interim analyses.			
	AT-4	When reporting adaptive randomized clinical trials, use the CONSORT statement, with modifications.	No	NA	
Standards for Studies of Medical Tests	MT-1	Specify clinical context and key elements of the medical test.	No	NA	
	MT-2	Assess the effect of factors known to affect performance and outcomes.	No	NA	
	MT-3	Focus studies of medical tests on patient-centered outcomes, using rigorous study designs with a preference for randomized controlled trials.	No	NA	
Standards for Systematic Reviews	SR-1	Adhere to National Academy of Medicine (NAM) standards for systematic reviews of comparative effectiveness research, as appropriate.	No	NA	

Standards on Research Designs Using Clusters	RC-1	Specify whether the study objectives, the interventions, and the primary outcomes pertain to the cluster level or the individual level.	No	NA	
	RC-2	Justify the choice of cluster randomization.	No	NA	
	RC-3	Power and sample size estimates must use appropriate methods to account for the dependence of observations within clusters and the degrees of freedom available at the cluster level.	No	NA	
	RC-4	Data analyses must account for the dependence of observations within clusters regardless of its magnitude.	No	NA	
	RC-5	Stratified randomization should be used when feasible.	No	NA	
Standards for Studies of Complex Interventions	SCI-1	Fully describe the intervention and comparator	No	NA	

		and define their core functions.			
	SCI-2	Specify the hypothesized causal pathways and their theoretical basis.	No	NA	
	SCI-3	Specify how adaptations to the form of the intervention and comparator will be allowed and recorded.	No	NA	
	SCI-4	Plan and describe a process evaluation.	No	NA	
	SCI-5	Select patient outcomes informed by the causal pathway.	No	NA	
Standards for Qualitative Methods	QM-1	State the qualitative approach to research inquiry, design, and conduct.	No	NA	
	QM-2	Select and justify appropriate qualitative methods sampling strategy.	No	NA	

	QM-3	Link the qualitative data analysis, interpretations, and conclusions to the study question.	No	NA	
	QM-5	Establish trustworthiness and credibility of qualitative research.	No	NA	
Standards for Mixed Methods Research	MM-2	Specify how mixed methods are integrated across design, data sources, and/or data collection phases.	No	NA	
	MM-2	Select and justify appropriate mixed methods sampling strategy.	No	NA	
	MM-3	Integrate data analysis, data interpretation, and conclusions.	No	NA	
Standards for Individual Participant-Level Data Meta-Analysis (IPD-MA)	IPD-1	Specify the research question(s) that will be addressed through the IPD-MA and describe the specific information it will provide that other approaches would not.	No	NA	

	IPD-2	Describe the proposed governance structure for the IPD-MA in the protocol and study reports.	No	NA	
	IPD-3	Use systematic, reproducible methods to identify studies for inclusion in the IPD-MA.	No	NA	
	IPD-4	Specify the design and planned analyses of the IPD-MA in a protocol, document any changes, and report significant amendments and modifications.	No	NA	