Supplemental File 1: eMethods

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) 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.[43]

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.[44,45] Additionally, it is not uncommon for abstracts that are published as part of conference proceedings to have inconsistencies when compared with the final study publication or to describe studies that are never published as full articles.[46-49]
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 only included outcome data from the report with the largest number of 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 follow-up data for an outcome.
4. **English language.** The compressed timeframe for this review did not permit translation of non-English language articles.

Study Design Criteria

1. We only included empirical studies; thus, we excluded reviews, letters, guidelines, position statements, and commentaries. We only used systematic reviews to identify empirical studies, as a supplement to the full literature search described in the section below entitled 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 randomized to groups, nor did we require that studies plan their comparison(s) prospectively. If, for a given treatment, there are no such studies, we then 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 only required outcome data 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 Syndrome as their primary diagnosis. We excluded patients being treated primarily for the following conditions at enrollment: non-epileptic seizures, metabolic seizures, or other seizures not due to epilepsy. In addition, as this review is intended to focus primarily on non-acute 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 only reported outcome data for a heterogeneous set of treatments (e.g., different infants receiving different pharmacologic agents, or 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 usage of the diet was based solely on parent report.
3. For gene therapy, we only included treatment for the following conditions: Dravet Syndrome, Angelman syndrome, and Rett syndrome.

Included Interventions

Category	Interventions	Interventions	Interventions
Pharmacological	Brivaracetam	Felbamate	Pregabalin
	Cannabidiol	Fenfluramine	Primidone
	Carbamazepine	Gabapentin	Rufinamide
	Clobazam	Lacosamide	Stiripentol
	Clonazepam	Lamotrigine	Tiagabine
	Diazepam	Levetiracetam	Topiramate
	Divalproex	Oxcarbazepine	Valproate
	Eslicarbazepine	Perampanel	Vigabatrin
	Ethosuximide	Phenobarbital	Zonisamide
	Everolimus	Phenytoin	
Dietary therapy	Ketogenic diet	Low glycemic index	Medium-chain triglyceride diet
	Modified Atkins	Modified ketogenic diet	
Surgery	Corpus callosotomy	Hemispherectomy/ Hemispherotomy	Resective surgery
	Laser ablation	Multiple subpial transections	
Brain 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.[50]
2. For effectiveness/comparative effectiveness, we only included studies with follow-up 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 (infection, new neurological deficits, surgical complications, irritability, somnolence, dizziness, drug toxicity, etc.)

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 outcomes that received strength-of-evidence (SOE) grades (seizure freedom, seizure frequency, adverse effects, hospitalization, all-cause mortality, SUDEP, quality of life, and caregiver quality of life), 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 follow-up, 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?

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