Pharmacologic and Dietary Treatments for Epilepsies in Children Aged 1–36 Months

A Systematic Review

Jonathan R. Treadwell, PhD, Sudha Kilaru Kessler, MD, MSCE, Mingche Wu, MPH,
Nicholas S. Abend, MD, MSCE, Shavonne L. Massey, MD, MSCE, and Amy Y. Tsou, MD, MSc

Correspondence
Dr. Treadwell
jtreadwell@ecri.org

Abstract

Background and Objectives

Early life epilepsies are common and often debilitating, but no evidence-based management guidelines exist outside of those for infantile spasms. We conducted a systematic review of the effectiveness and harms of pharmacologic and dietary treatments for epilepsy in children aged 1–36 months without infantile spasms.

Methods

We searched EMBASE, MEDLINE, PubMed, and the Cochrane Library for studies published from January 1, 1999, to August 19, 2021. Using prespecified criteria, we identified studies reporting data on children aged 1–36 months receiving pharmacologic or dietary treatments for epilepsy. We did not require that studies report etiology-specific data. We excluded studies of neonates, infantile spasms, and status epilepticus. We included studies administering 1 of 29 pharmacologic treatments and/or 1 of 5 dietary treatments reporting effectiveness outcomes at ≥ 12 weeks. We reviewed the full text to find any subgroup analyses of children aged 1–36 months.

Results

Twenty-three studies met inclusion criteria (6 randomized studies, 2 nonrandomized comparative studies, and 15 prestudies/poststudies). All conclusions were rated low strength of evidence. Levetiracetam leads to seizure freedom in some infants (32% and 66% in studies reporting seizure freedom), but data on 6 other medications were insufficient to permit conclusions about effectiveness (topiramate, lamotrigine, phenytoin, vigabatrin, rufinamide, and stiripentol). Three medications (levetiracetam, topiramate, and lamotrigine) were rarely discontinued because of adverse effects, and severe events were rare. For diets, the ketogenic diet leads to seizure freedom in some infants (rates 12%–37%), and both the ketogenic diet and modified Atkins diet reduce average seizure frequency, but reductions are greater with the ketogenic diet (1 RCT reported a 71% frequency reduction at 6 months for ketogenic diet vs only a 28% reduction for the modified Atkins diet). Dietary harms were not well-reported.

Discussion

Little high-quality evidence exists on pharmacologic and dietary treatments for early life epilepsies. Future research should isolate how treatments contribute to outcomes, conduct etiology-specific analyses, and report patient-centered outcomes such as hospitalization, neurodevelopment, functional performance, sleep quality, and patient and caregiver quality of life.

Trial Registration Information

This systematic review was registered in PROSPERO (CRD42021220352) on March 5, 2021.

From the ECRI-Penn Medicine Evidence-based Practice Center (J.R.T., M.W., A.Y.T.), ECRI, Plymouth Meeting, PA; Department of Pediatrics (Division of Neurology) (S.K.K., N.S.A., S.L.M.), Children's Hospital of Philadelphia; Departments of Neurology and Pediatrics (S.K.K., N.S.A., S.L.M.), University of Pennsylvania Perelman School of Medicine; Department of Anesthesia & Critical Care (N.S.A.), University of Pennsylvania Perelman School of Medicine; Department of Biostatistics, Epidemiology and Informatics (N.S.A.), University of Pennsylvania Perelman School of Medicine; and Division of Neurology (A.Y.T.), Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, PA.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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Glossary

AHRQ = Agency for Healthcare Research and Quality; **ASM** = antiseizure medication; **ILAE** = International League Against Epilepsy; **MAD** = modified Atkins diet; **RCTs** = randomized controlled trials; **SOE** = strength of evidence; **SR** = systematic review.

Epilepsy is one of the most common neurologic disorders of childhood,[1] with high incidence in the first year of life.[2,3] The underlying etiologies, clinical presentations, electroencephalographic patterns, treatment strategies, and effects differ substantially in epilepsies occurring in early life compared with that occurring in older children or adults. Early life epilepsy is often associated with concurrent neurodevelopmental impairment and treatment resistance.[4] Development may be affected by pathophysiology of underlying disease, ongoing seizures, or treatment adverse effects; however, the relative contribution of these factors is unclear. Improved understanding of molecular and cellular mechanisms of specific etiologies of early life epilepsies has supported increasingly nuanced treatment approaches. However, epilepsy precision therapy remains nascent, and no mechanistically specific therapy is available for most patients with epilepsy. Therefore, selecting a treatment strategy requires careful consideration of risks and benefits, particularly given uncertainties regarding efficacy and potential adverse effects.[5]

Treatment selection in young children remains highly variable, even for first-line antiseizure medication (ASM) monotherapy. A 2017 multicenter study[6] of 495 children with nonsyndromic epilepsy diagnosed before the age of 36 months found levetiracetam was the first-line ASM for most of the patients; however, rates varied widely from 29% to 75% across centers. This variability may reflect key evidence gaps around optimal treatment. In 2015, the International League Against Epilepsy (ILAE) released a consensus report on recommendations for the management of infantile seizures, which concluded no contemporary ASMs are supported by high-quality evidence.[4] Other systematic reviews of epilepsy treatment, including a 2020 update by the National Institute for Health Care Excellence,[7] have addressed the broader population without focusing on early life epilepsy specifically.

To address these key evidence gaps for the treatment of early-life epilepsy, the American Epilepsy Society, in partnership with the Agency for Healthcare Research and Quality (AHRQ) and the Patient-Centered Outcomes Research Institute, sponsored this systematic review (SR) assessing the treatment of epilepsy in young children aged 1–36 months. Specifically, we assessed the effectiveness and harms of pharmacologic interventions, dietary interventions, surgical interventions, neuromodulation, and gene therapy for selected conditions. The full AHRQ report is available at https://effectivehealthcare.ahrq.gov/products/management-infantile-epilepsy/research. This article summarizes evidence on pharmacologic and dietary treatments, and a companion article examines surgical procedures.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The review protocol was posted on the AHRQ website for public comment and registered in PROSPERO (CRD42021220352). Neither trial registration nor patient consent was applicable because this was an SR.

Scope, Search, and Inclusion Criteria

To inform scope and methods, we incorporated feedback from 9 stakeholders including child neurologists, neurosurgeons, dietitians, and nurse practitioners. A professional information specialist searched EMBASE, MEDLINE, PubMed, and the Cochrane Library (see eMethods, links.lww.com/WNL/C433 for full search strategy) for studies published from January 1, 1999, to August 19, 2021.

The eMethods, links.lww.com/WNL/C433, provides full inclusion criteria and extracted outcomes. For inclusion, studies were required to assess specific pharmacologic or dietary interventions as epilepsy treatment in children 1–36 months of age. Studies with mixed etiologies and specific etiologies (e.g., Dravet syndrome) were included. Key outcomes included seizure freedom, seizure frequency reduction, adverse effects, hospitalization, all-cause mortality, sudden unexplained death in epilepsy, patient quality of life, and caregiver quality of life. We excluded neonates because neonatal seizures are considered distinct-based physiologic and etiologic differences in this age group.[8] We also excluded studies assessing treatments for provoked seizures (e.g., febrile seizures), metabolic epilepsies, status epilepticus, and acute symptomatic seizures. In addition, infantile spasms were excluded because of a relatively well-defined evidence base[4,9-14] and unique treatment considerations. We did not require EEG confirmation of seizures. If studies reported a mix of patient ages or seizure types, we required the study to either (1) include ≥80% relevant population or (2) report relevant data separately as a subgroup.

We considered all study designs. For inclusion, randomized controlled trials (RCTs) and nonrandomized studies were required to report data on ≥10 or ≥30 infants per arm, respectively. For effectiveness outcomes, studies were required to report outcomes at ≥12 weeks; for harm outcomes, there was no minimum follow-up.

Screening, Extraction, and Analysis

Two analysts independently screened each abstract in Distiller, with disagreements resolved by consensus. We extracted data from included studies into Microsoft Excel. For a predetermined list of key outcomes, we rated the risk of bias using Cochrane Risk of Bias

2 for RCTs,[15] the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) instrument for nonrandomized studies with control groups,[16] and Evidence-based Practice Center guidance for studies without control groups.[17] For key outcomes, we also rated strength of evidence (SOE) using the 2013 AHRQ Methods Guide recommendations,[18] which use domains including study design, risk of bias, consistency of results across trials, directness of the evidence, and precision of effect estimate.

Data Availability

All data for the full report are available at effectivehealthcare.ahrq.gov/.

Results

Evidence Base

Searches identified 11,123 potential citations. After title and abstract screening, 41 studies met inclusion criteria, including 15 addressing pharmacologic treatments and 8 addressing dietary treatments. Common reasons for full-text exclusions were as follows: (1) <80% in age group of interest, (2) <30 patients in nonrandomized studies, and (3) focus on neonates. Study details and treatment/patient characteristics are summarized in eTables 1–4, links.lww.com/WNL/C434.

Effectiveness of Pharmacologic Treatments

Twelve studies were included for effectiveness data; the other 3[19-21] were only included for harms (all 15 are listed in Table 1). Drugs assessed include levetiracetam, topiramate, lamotrigine, phenytoin, vigabatrin, rufinamide, and stiripentol. Treatment was first-line (4 studies), add-on (6 studies), and a mixture of first-line, add-on, and subsequent monotherapy (2 studies). Figure 1 shows seizure freedom data, and Table 2 summarizes the SOE ratings.

Levetiracetam

Four studies described the effectiveness or comparative effectiveness of levetiracetam. We concluded that levetiracetam may cause seizure freedom in some patients (based on low strength of evidence).

One RCT randomized treatment-naive infants to *valproate* (N = 50) or *valproate and levetiracetam* (N = 50).[22] Valproate dosing was 40–50 mg/kg/d, and levetiracetam dosing was 20–30 mg/kg/d. At 12 weeks, infants receiving valproate and levetiracetam had better outcomes for all 8 measures: 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 Inventory 31 scores, mean 84 vs mean 60, scale range 0–100), daily living ability (Barthel index scores, mean 86 vs mean 62, scale range 0–100 where higher scores are better), and 3 cognitive ability scales. The study used several outcome instruments not intended for young children (Mini-Mental State Examination, Weschler Memory Scale-Revised in China, Quality of Life in Epilepsy 31, and Barthel instrument). We were unable to determine whether authors modified the instruments for use in young children. However, because no conclusions were based on these outcomes, their inclusion did not influence the main findings.

Another study performed a prospective prestudy/poststudy of 101 infants with mixed etiologies.[23] Levetiracetam (mean daily dose 46 mg/kg/d) was added to existing medications. At a mean of 5 months on levetiracetam, investigators considered both seizure type and seizure frequency in rating each infant on a 1–7 scale (1 = marked worsening and 7 = marked improvement). Improvement was marked in one-third of infants (33%, 28/85), moderate in 26% (22/85), slight in 13% (11/85), and either no change or seizure worsening in 28% (24/85). Clinicians judged changes in psychomotor development using the same 1–7 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 48% (40/85).

A third study performed a retrospective prestudy/poststudy of 92 treatment-naive infants (56% with unknown etiologies) who had received levetiracetam (10–60 mg/kg/d, including 52% taking 30–40 mg/kg/d).[24] At a median of 12 months, 66% of infants were seizure-free.

Based on these studies, we concluded that levetiracetam causes seizure freedom in some infants (SOE: low).

For comparative effectiveness, one study retrospectively compared outcomes of monotherapy with levetiracetam (N = 117; median target dose 25 mg/kg/d) or phenobarbital (N = 38; median target dose 5 mg/kg/d) for first-line treatment of nonsyndromic epilepsy.[25] The only outcome reported was "freedom from monotherapy failure," defined as no seizures 4–6 months after treatment initiation and no second ASM other than pyridoxine prescribed during the 6 months after treatment initiation. The unadjusted rates were 40% for levetiracetam (47/117) and 16% (6/38) for phenobarbital (OR 3.6, 95% CI 1.5–10, favoring levetiracetam). Owing to the nonrandomized design, the authors conducted numerous additional analyses to control for selection bias, all of which favored levetiracetam over phenobarbital. The authors' best estimate was a propensity score–based OR of 4.2 (95% CI 1.1–16).

Topiramate

We included 3 studies on the effectiveness of topiramate (all mixed etiologies). We drew no conclusions due to low-quality study designs (pre/post, nonrandomized) and inconsistent results.

One study enrolled treatment-naive infants with unspecified etiologies receiving either topiramate (N = 41; 3–9 mg/kg/d) or carbamazepine (N = 105; 5–30 mg/kg/d).[26] The article did not report how the choice was made. At 6 months, ≥50% seizure reduction rates were 73% and 63%, and seizure freedom rates were 59% and 55% for topiramate and carbamazepine, respectively.

Another study performed a retrospective prestudy/poststudy of adjunctive topiramate that included a subgroup of 58 infants aged 1 year or younger.[27] Age, seizure type, and dose

Table 1 Overview of Included Pharmacologic Studies

| Study	Intervention(s)	N and mean age at start	Etiologies	Seizure types
Liu et al. (2020)[22] RCT, first-line	Valproate vs valproate + levetiracetam	N = 100 2 y	NR	NR
Arzimanoglou et al. (2016)[23] pre/post, mix of first-line, add-on and other	Levetiracetam	N = 101 6 mo	Various, and none more than 20% (eTable 2, links.lww.com/WNL/C434)	Various, and none more than 25% (eTable 2, links.lww.com/WNL/C434)
Arican et al. (2018)[24] pre/post, first-line	Levetiracetam	N = 92 6 mo	Structural 21%, metabolic 11%, genetic 9%, infectious 3%, unknown 56%	Focal 58%, generalized 42%
Grinspan et al. (2018)[25] Nonrandomized comparative study, first-line	Levetiracetam vs phenobarbital	N = 155 NR	Nonsyndromic epilepsy 60% and 42%, unknown etiology 17% and 32%, others 23% and 24%	Focal 56% and 61%, generalized 25% and 21%, mixed or unclear 19% and 18%
Kim et al. (2009)[26] Nonrandomized comparative study, first-line	Topiramate vs carbamazepine	N = 146 10 and 8 mo	Underlying pathology in 46% and 32%	Partial 20% and 44%, generalized 71% and 47%, unclassified 10% and 10%
Kholin et al. (2014)[27] pre/post mix of first-line, add-on and other	Topiramate	N = 58 All were <1 y	Mixed, but most common were symptomatic/cryptogenic frontal epilepsy (30%) and symptomatic/cryptogenic temporal epilepsy (22%).	NR
Grosso et al. (2005)[28] pre/post, add-on	Topiramate	N = 36 13 mo	Various, and none more than 27% (eTable 2, links.lww.com/WNL/C434)	Various, and none more than 22% (eTable 2, links.lww.com/WNL/C434)
Kim et al. (2010)[19] pre/post, add-on, (only included for harms data)	Topiramate	N = 81 All were younger than 1 y	NR	NR
Novotny et al. (2010)[21,35] RCT, add-on (only included for harms data)	Topiramate (3 doses) vs Placebo	N = 149 10–13 mo	NR	All had partial seizures, 13% were also having generalized seizures
Manitpisitkul et al. (2013)[20] RCT, add-on, (only included for harms data)	Topiramate (compared 4 doses)	N = 55 11–12 mo	NR	Various. Most in each group had partial seizures; (eTable 2, links.lww.com/WNL/C434)
Piña-Garza et al. (2008)[29,30] withdrawal RCT, add-on	Lamotrigine	N = 204 16 mo	NR	Various (eTable 2, links.lww.com/WNL/C434)
Sicca et al. (2000)[31] pre/post, add-on	Phenytoin	N = 55 7 mo	Various, and none more than 13% (eTable 2, links.lww.com/WNL/C434)	Generalized epilepsy 51%, partial epilepsy 49%
Jackson et al. (2017)[32] pre/post, add-on	Vigabatrin	N = 103 8 mo	Structural/metabolic 49.5%, TSC 24%, malformation of cortical development 18%, other 8%	91% "epileptic spasms"
Tanritanir et al. (2021)[33] pre/post	Rufinamide	N = 103 20 mo	Various, and none more than 32% (eTable 2, links.lww.com/WNL/C434)	Various (eTable 2, links.lww.com/WNL/C434)
Yamada et al. (2021)[34] pre/post, add-on	Stiripentol	N = 95 Range 0–2 y	NR	NR

Abbreviations: mo = month; NR = not reported; RCT = randomized controlled trial; TSC = tuberous sclerosis complex; y = years.

were not reported for this subgroup. Among 58 infants, 55% had ≥50% reduction in seizure frequency of which 19% were seizure-free (time point not reported).

Another study performed a prospective prestudy/poststudy of adjunctive topiramate in 59 children refractory to ≥1

ASM.[28] On average, patients received 5.2 mg/kg/d. The study included a subgroup of 37 infants (median age 11 months). The dose and seizure types were not reported for this subgroup. Three months after starting topiramate, 3 of 37 (8%) were seizure-free, and 20 of 37 (54%) experienced a ≥50% seizure reduction.

Figure 1 Rates of Seizure Freedom After Pharmacologic Treatments

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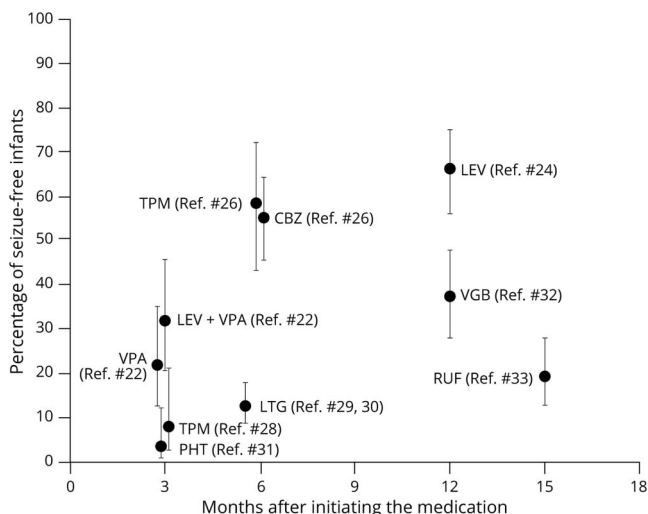
Lamotrigine

One study assessed the effectiveness of lamotrigine. We drew no conclusions because there was only 1 study of low-quality design (prefollow-up/postfollow-up of an RCT).

The study was a withdrawal randomized trial of lamotrigine vs placebo[29,30] All infants first received lamotrigine. Lamotrigine responders (children with ≥40% seizure frequency reduction) were randomized to continue lamotrigine or receive a placebo substitution. However, because the placebo comparison period was at most 8 weeks, the randomized phase of the study did not meet inclusion criteria for effectiveness data. Instead, for effectiveness, we included the long-term prepost data reported by the long-term open-label follow-on publication. The open-label study enrolled 204 infants (mean age 15.9 months at treatment initiation) with partial seizures not successfully controlled on at least 1 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/d for those on either valproate or a nonenzyme-inducing ASM or 15.6 mg/kg/d for those on enzyme-inducing ASM. At 24+ weeks' follow-up, 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

One study assessed the effectiveness of phenytoin. We drew no conclusions because there was only 1 study of low-quality design (pre/post).

The study used a prestudy/poststudy design of 55 infants treated with oral phenytoin.[31] Thirty-three first received phenytoin intravenously for status epilepticus and continued receiving oral

phenytoin for seizure prophylaxis, whereas the other 22 infants were treated only with oral phenytoin for prophylaxis. At 3 months, the rate of seizure freedom was 4% (2/55), and the rate of ≥50% reduction in seizure frequency was 9% (5/55).

Vigabatrin

One study included assessed the effectiveness of vigabatrin. We drew no conclusions because there was only 1 study of low-quality design (pre/post).

The study reported data on 103 infants (mean age 8 months at treatment initiation) treated with vigabatrin (median dose 93.8 mg/kg/d at the last follow-up, which occurred after approximately 1 year of vigabatrin treatment).[32] At an average of 1 year on vigabatrin, 38% of infants were seizure-free (33/88 with long-term follow-up data), 73% of infants had ≥50% reduction in seizure frequency, and the median percentage reduction in seizures was 97% (interquartile range [IQR] 43%–100%; baseline seizure frequency not reported).

Rufinamide

One study assessed the effectiveness of rufinamide. We drew no conclusions because there was only 1 study of low-quality design (pre/post).

The study performed a prestudy/poststudy of 103 infants (median age 20 months at treatment initiation) treated with rufinamide (median dose 42 mg/kg/d at the last follow-up, which occurred at median of 15 months).[33] At a median of 15 months of treatment, 19% (20/103) were seizure-free, and 50% (51/103) experienced ≥50% reduction in seizure frequency. The median percentage reduction in seizures was 54% (from ~167/mo at baseline to 90/mo at follow-up). Rufinamide was discontinued because of a lack of efficacy in 23% (24/103).

Stiripentol

One study assessed the effectiveness of stiripentol in young children with Dravet syndrome. We drew no conclusions because there was only 1 study of low-quality design (pre/post).

The study reported a subgroup analysis of 95 infants with Dravet syndrome aged 0–2 years receiving stiripentol.[34] The dose for this 0–2 years age subgroup was not reported, but for the larger population of 376 patients, the median dose after 1 year was 32.5 mg/kg/d. The only reported effectiveness outcome was physician's judgment of degree of improvement rated on a 1–5 scale (1 = marked, 2 = moderate, 3 = mild, 4 = no change, and 5 = worsened) based on seizure frequency, duration, intensity, and ability to undertake activities of daily living. At 2 years, 54% (50/92) were rated as having either "marked" or "moderate" improvement.

Harms of Pharmacologic Treatments

Twelve studies reported on the harms of 7 pharmacologic treatments (the same 7 in the effectiveness section); 3 pharmacologic studies[25,27,28] did not report whether harms occurred.

Table 2 Strength of Evidence for Effectiveness of Pharmacologic and Dietary Interventions

Treatment	Outcome	Study findings	Strength of evidence	Conclusion
Pharmacologic interventions				
Levetiracetam	Seizure freedom	One RCT[22] (N = 100) reported seizure freedom rates of 32% (16/50) with LEV+ valproate vs 22% (11/50) with valproate alone (OR 1.7, 95% CI 0.7–4.1) One prestudy/poststudy[24] reported 66% seizure freedom (61/92)	Low	Adding levetiracetam causes seizure freedom in some infants
	Quality of life	One RCT[22] (N = 100) reported QOL scores of 84 with LEV+ valproate vs 60 valproate alone (a 12-week follow-up) (statistically significant)	Insufficient	NA
Topiramate	Seizure freedom	One nonrandomized comparative study[26] reported 59% seizure freedom (24/41) One prestudy/poststudy[27] reported 19% seizure freedom (11/58) One prestudy/poststudy[28] reported 8% seizure freedom (3/37)	Insufficient	NA
Topiramate vs carbamazepine	Seizure freedom	One nonrandomized comparative study[26] (N = 146) reported the following rates of seizure freedom: topiramate 59% (24/41) vs carbamazepine 55% (58/105)	Insufficient	NA
Lamotrigine	Seizure freedom	One prestudy/poststudy[30] reported 13% seizure freedom (26/204)	Insufficient	NA
Phenytoin	Seizure freedom	One prestudy/poststudy[31] reported 4% seizure freedom (2/55)	Insufficient	NA
Vigabatrin	Seizure freedom	One prestudy/poststudy[32] reported 38% seizure freedom (33/88)	Insufficient	NA
Rufinamide	Seizure freedom	One prestudy/poststudy[33] reported 19% seizure freedom (20/103)	Insufficient	NA
Rufinamide	Seizure frequency	One prestudy/poststudy[33] reported median 54% reduction in seizure frequency	Insufficient	NA
Dietary interventions				
Ketogenic diet	Seizure freedom	One RCT[37] compared KD with MAD and reported 9 of 17 (53%) patients were seizure-free at both time points. Three prestudies/poststudies[39,41,43] reported seizure freedom rates ranging from 12% to 37% at 3–12 mo	Low	Ketogenic diet causes seizure freedom in some infants
Ketogenic diet	Seizure frequency	One RCT[38] reported KD statistically significantly reduced seizure frequency by 57.95 ± 17.73 compared with control at 3 mo and by 70.79 ± 19.26 at 6 mo. One RCT[37] and 5 prestudies/poststudies[39,41-44] reported rates of ≥90% reduction ranging from 2% to 53% at 3–12 mo and rates of ≥50% reduction ranging from 33% to 85%	Low	Ketogenic diet reduces seizure frequency
Modified Atkins diet	Seizure freedom	One RCT[37] reported 4 of 20 patients seizure-free at 3 mo and 5 of 20 patients seizure-free at 6 mo.	Insufficient	NA
Modified Atkins diet	Seizure frequency	One RCT[38] found that compared with controls (n = 10), MAD (n = 15) reduced seizure frequency (28% vs 8%, MAD and control, resp.) at 6 mo. One RCT[37] reported the MAD (n = 20) reduces the seizure frequency by 46.18% at 3 mo and 39.76% at 6 mo compared with that at baseline.	Low	MAD reduces seizure frequency.
Ketogenic diet vs Modified Atkins diet	Seizure freedom	One RCT[37] (n = 37) found that compared with MAD, patients receiving KD had higher rates of seizure freedom at 3 mo: 53% vs 20%, (OR 4.05, 95% CI 1.05–20). However, this difference was not statistically significant at 6 mo (53% vs 25%, OR 3.4, 95% CI 0.84–13.5).	Insufficient	NA
Ketogenic diet vs Modified Atkins diet	Seizure frequency	One RCT[38] (n = 40) found KD was more effective at reducing the seizure frequency than MAD at both 3 and 6 mo. One RCT[37] reported results in the same direction (favoring KD over MAD), but results were not statistically significant.	Low	KD reduces seizure frequency more than MAD

Abbreviations: CI = confidence interval; KD = Ketogenic diet; MAD = modified Atkins diet; mo = months; OR = odds ratio; RCT = randomized controlled trial.

Below, we have summarized adverse events (1) that resulted in study discontinuation, (2) that were deemed "serious" or "severe" by authors, (3) that resulted in dose modification, or (4) with data that suggested a dose-response association. Other events are described in the full AHRQ report.

Levetiracetam

A prestudy/poststudy reported 7% of patients (7/101) experienced at least 1 treatment-emergent adverse event leading to study discontinuation, and 5 of the 7 events involved respiratory problems.[23] In addition, 12% of patients (12/101)

had a "severe" adverse event (authors did not report whether any of the 12 were respiratory), and none were considered by the clinician to be related to levetiracetam. "Serious" events occurred in 32% (32/101), but only 2 (both convulsions) were considered levetiracetam-related (authors did not define severe and serious). Furthermore, 10% (10/101) had an adverse event that required dose modification.

A prestudy/poststudy of 92 patients reported no patients discontinued because of adverse events.[24] The study made no statements about any adverse events that were serious, severe, or required dose modification.

The RCT comparing valproate alone with valproate+ levetiracetam.[22] did not explicitly report any critical harms. Effectiveness data were reported for all enrolled patients at 12 weeks, so likely there were no <12-week discontinuations due to adverse events. Overall, one of the 3 studies[23] suggests that levetiracetam may cause respiratory events.

Topiramate
Three studies reported low rates for discontinuation due to adverse events (4%, 6%, and 12%) and serious/severe events (infections and aggravated convulsions; 0%, 8%, and 12%), with no dose-response association. For less severe events occurring in at least 10% of patients, 2 RCTs found dose-response associations for 2 events: loss of appetite (8%–11% with 5–15 mg/kg/d, but 16%–20% with 25 mg/kg/d) and upper respiratory tract infection (1 RCT of 4 doses found a steady increase in the rate from 0% to 38% as dose increased from 3 to 25 mg/kg/d). For 3 other less severe events (bronchitis, vomiting, and weight decrease), one RCT[20] found a dose-response association; however, another RCT[21,35] found no association between topiramate and any of those 3 events.

One study found that of 81 infants receiving topiramate, hypohydrosis occurred in 48% (39/81).[19] Another study[26] reported that 2% (1/41) of infants had anhidrosis. Neither RCT[20,35] reported rates of hypohydrosis or anhidrosis.

Other Pharmacologic Treatments
The lamotrigine RCT reported that during the 8-week randomized phase, none of the 38 patients discontinued lamotrigine because of adverse events.[29,30] However, this study phase included only patients who had demonstrated tolerability during an initial 5-week open-label phase. During the long-term open-label phase, 9% of patients (18/204) discontinued lamotrigine because of adverse events. The authors reported details for 15 of the 18 discontinuations: pneumonia (n = 4), complex partial seizures (n = 3), status epilepticus (n = 3), rash (n = 3), and fever (n = 2).

Regarding serious events, 2 events occurred in the randomized phase: 1 patient who received lamotrigine (5%, 1/19) had serious bronchitis, and 1 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 a convulsion, 3% (6/204) had dehydration, and 3% (12/204) had gastroenteritis.

The phenytoin study reported no patients discontinued the medication because of adverse events, and no patients experienced any serious or severe events.[31]

The vigabatrin study 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).[32] The study did not report rates of severe or serious adverse events. Before vigabatrin administration, 69% (34/49) had vision abnormalities, which authors attributed to tuberous sclerosis complex, refractive errors, and prior medication. During vigabatrin use, 81% (50/62) had at least 1 abnormal examination. After the withdrawal of vigabatrin, 63% (31/49) had vision abnormalities (a similar rate to that before vigabatrin initiation). Overall, some evidence suggests that vigabatrin may cause temporary vision abnormalities, but given that only a single prestudy/poststudy has addressed the issue, strong conclusions cannot be drawn.

Effectiveness of Dietary Treatments
Eight studies addressed the effectiveness of dietary treatments (Table 3). Figure 2 shows relevant seizure freedom data, and Table 2 summarizes SOE ratings. All studies enrolled mixed etiologies, and 7 enrolled patients receiving multiple ASMs without sufficient effectiveness (diets were added to existing ASM). We excluded one RCT[36] because only a small percentage of enrolled patients were ages 1–36 months, and no subgroup analyses for this age group was reported (only 46% of children were aged 2–6 years; the other 54% were older than years).

Ketogenic Diet
Five studies[37-41] used a 4:1 ratio of lipids to nonlipids, and the other 3[42-44] used lower ratios (1:1 to 3:1). Three studies used no initial fasting period, 1 used a 1-day initial fasting period, and 4 did not mention initial fasting.

One RCT compared KD with no dietary change.[38] They also included a modified Atkins diet (MAD) group (discussed further). The classic 4:1 KD was provided, and all infants maintained the same doses of ASM (valproic acid, carbamazepine, and/or clonazepam). At both 3 and 6 months, KD was more effective than control (no dietary change) for reducing both seizure frequency (3 months mean 58% decrease vs 6% increase, 6 months mean 71% decrease vs 8% decrease) and seizure severity (Chalfont scale; 3 months 32% vs 0.5% and 6 months 36% vs 2%).

Another RCT compared KD (4:1 using the Johns Hopkins protocol) with MAD in 37 infants with at least 2 ASM failures.[37] In the KD group, the rate of seizure freedom was 53% at both 3 and 6 months, and at both time points, 59%

Table 3 Overview of Included Dietary Studies

Study	Interventions	N and mean age at start	Etiologies	Seizure types
Kim et al. 2015[37] RCT	Ketogenic diet (classic) 4:1 vs Modified Atkins diet	N = 37 1–2 y	Various (eTable 4, links.lww.com/WNL/C434)	Various (eTable 4, links.lww.com/WNL/C434)
El-Rashidy et al. 2013[38] RCT	Ketogenic diet (classic) 4:1 vs Modified Atkins diet vs no change in diet	N = 40 26–27 mo	Various (eTable 4, links.lww.com/WNL/C434)	Various (eTable 4, links.lww.com/WNL/C434)
Kim et al. 2019[42] pre/post	Ketogenic diet ranging from 1:1 to 3:1	N = 49 1.4 y	None had West syndrome; others NR	NR
Dressler et al. 2015[43] pre/post	Ketogenic diet (classic) ranging from 2.5:1 to 4:1	N = 58 0.68 y	Various (eTable 4, links.lww.com/WNL/C434)	Various (eTable 4, links.lww.com/WNL/C434)
Wu et al. 2015[39] pre/post	Ketogenic diet (classic) 4:1	N = 40 85% were age 1–3	Various (eTable 4, links.lww.com/WNL/C434)	Various (eTable 4, links.lww.com/WNL/C434)
Suo et al. 2012[40] pre/post	Ketogenic diet (classic) 4:1	N = 147 0–2 y	NR	NR
Kang et al. 2005[41] pre/post	Ketogenic diet (classic) 4:1	N = 49 All <2 y	Various (eTable 4, links.lww.com/WNL/C434)	Various (eTable 4, links.lww.com/WNL/C434)
Liu et al. 2021[44] pre/post	Ketogenic diet (classic) ranging from 2:1 to 4:1	N = 41 20.51 mo	NR	NR

Abbreviations: NR = not reported; RCTs = randomized controlled trials.

experienced a ≥50% seizure reduction. In 5 prestudies/poststudies (3- to 12-month follow-up), seizure freedom rates ranged from 12% to 37%, and the rate of ≥50% seizure reduction ranged from 33% to 85%.[39,41-44]

Modified Atkins Diet

One RCT reported that, compared with no change in diet, the MAD demonstrated statistically significantly greater reduction in seizure frequency at 6 months (mean reductions 28% vs 8%) but not at 3 months (mean reductions 7% vs 6%).[38] Seizure severity data (as measured by the Chalfont score) statistically significantly favored MAD (vs no dietary change) at both 3 months (16% vs 0.5% improvement) and 6 months (38% vs 2% improvement).

Ketogenic Diet vs MAD

Both RCTs[37,38] compared KD with MAD. One RCT[38] found higher rates of seizure freedom with KD than with MAD at 3 months (53% vs 20%), but the difference was not statistically significant at 6 months (53% vs 25%). For seizure frequency reduction, the same RCT[38] reported an advantage of KD over MAD at both 3 months (58% vs 7%) and 6 months (71% vs 28%), and the other RCT[37] reported statistically nonsignificant results in the same direction (81% vs 54% at 3 months and 100% vs 60% at 6 months). For seizure severity, one RCT[38] reported statistically nonsignificant results in percentage improvements at both 3 months (32% KD and 16% MAD) and 6 months (36% KD and 38% MAD).

Harms of Dietary Treatments

Ketogenic Diet

Four studies reported on harms.[38,42-44] Regarding withdrawal due to side effects or diet intolerance, one study[42] found a rate of 2% (2/109) and one RCT[38] found a rate of 20% (2/10).

Figure 2 Rates of Seizure Freedom After Dietary Treatments
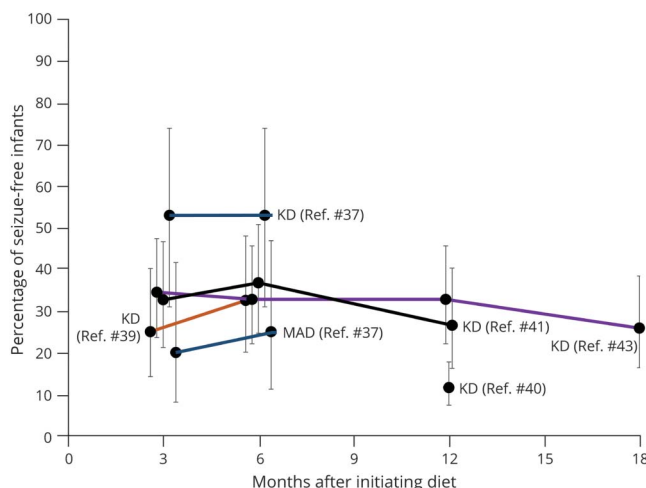
One study also reported 32% constipation (35/109), 33% decreased HCO3 level (36/109), and 20% vomiting/reflux (22/109), and 4 other events were experienced by <10% of patients (low free carnitine level, feeding difficulty, kidney stone, and transient hypoglycemia).[42] One study reported that 50% (29/58) of patients experienced "side effects" but did not report specifics and noted that there was "difficulty introducing solid foods" in 28% (16/58).[43] One study reported low rates of constipation (20%), diarrhea (10%), and dysphagia (10%).[38]

One study reported that at 1 year after KD initiation, the percentage of patients who were overweight/obese decreased significantly from 17% at baseline (7/41) to 2% (1/41).[44] Other metrics (e.g., z score of body mass index for age) suggested short-term weight loss in many infants on KD, but the prechanges/postchanges were not statistically significant.

Modified Atkins Diet

One study reported harms for the MAD.[38] Thirteen percentage (2/15) of patients dropped out because of diet intolerance and "significant" weight loss; other adverse effects included vomiting (27%, 4/15), constipation (13%, 2/15), diarrhea (13%, 2/15), and dysphagia (20%, 3/15).

Discussion

Our SR found limited evidence on the effectiveness and safety of pharmacologic and dietary treatments for epilepsies in children aged 1–36 months. Although we included studies assessing 10 ASMs (levetiracetam, topiramate, lamotrigine, phenytoin, vigabatrin, valproate, phenobarbital, carbamazepine, rufinamide, and stiripentol), evidence is sufficient only to permit conclusions for a single drug, levetiracetam (SOE: low). One study found that freedom from monotherapy failure was more likely with levetiracetam than with phenobarbital.[25] Everolimus was on our list of included treatments, but no everolimus studies met inclusion criteria. Sodium channel blockers (included in the list above) were evaluated; the corresponding data did not exist, were not included, or were insufficient to permit conclusions.

For harms, we concluded 3 ASM s(levetiracetam, topiramate, and lamotrigine) rarely have adverse effects severe enough to warrant discontinuation. For topiramate, we did find consistent evidence of dose-dependent effects for 2 nonsevere adverse effects: loss of appetite and upper respiratory tract infection. Although parents worry about both short-term and long-term adverse effects from drugs,[45] studies rarely measured long-term outcomes.

Regarding dietary therapies, we concluded that the KD is effective for producing seizure freedom and reducing seizure frequency and is more likely to reduce seizure frequency than the MAD (SOE: low). Harms of diets were rarely reported, so we drew no conclusions about harms or dietary intolerance.

Our review highlights several limitations in the current body of literature. The 2015 ILAE Commission of Pediatrics also reported that evidence for treatment of infantile epilepsy was lacking, and recommendations were based on expert opinion survey data.[4] A major reason for these limitations was a lack of ASM studies that included early life epilepsies or a large enough subgroup to evaluate independently. Regulatory RCTs of newer ASM for disorders that first present in early life, such as Dravet syndrome, often include broad age ranges from early life to adulthood.[46,47] Mixed etiology studies did not report outcomes by etiology, perhaps due to sample sizes. Evidence on any specific treatment in this age group was often limited to single studies. The most common study design was a single-arm study, and authors typically attributed outcomes (e.g., seizure reductions) to the study treatments alone, rather than other possible explanations (e.g., other treatments, short follow-up time, and spontaneous variability).

Because direct evidence to support the development of a clinical practice guideline for early life epilepsy may be lacking, approaches for creating a guideline beyond expert opinion survey may include extrapolation of efficacy of data from older patients for certain seizure or epilepsy types. US Food and Drug Administration industry guidance[48] allows for extrapolation of efficacy data in partial (focal)–onset seizures down to the age of 1 month based on presumed mechanistic similarity across age groups, with regulatory approval for age extension requiring only safety and pharmacokinetic data. While extrapolation reduces regulatory burden, future guidelines should acknowledge the indirectness of efficacy evidence.

Evidence on the management of infantile spasms is more substantial[4,9-14] than the evidence for other early life seizure types or epilepsies and has been used to develop clinical practice guidelines–thus, our scoping process resulted in the exclusion of infantile spasms from this review.

Another substantial limitation of the literature highlighted by this review is the lack of reporting on treatment outcomes beyond seizure frequency, such as hospitalization, neurodevelopment, functional performance, or sleep quality. While these facets may have a greater effect than seizure frequency on quality of life in epilepsy, drug development has largely focused on antiseizure treatment, often narrowly defined as seizure frequency. In addition, for logistical and cost reasons, short-term outcome measurement predominates despite the greater importance of long-term outcomes.

As knowledge grows of the etiologically specific mechanisms of seizures and other manifestations of early life epilepsies, we expect future therapeutic research will focus on increasingly specific populations of patients with epilepsy. In future studies of ASM in patients with diverse etiologies and clinical syndromes, greater attention to reporting results by etiology and syndrome may address key questions about the applicability of outcome data to specific patient types in clinical practice. In addition, this report demonstrates the lack of attention to outcome measures beyond seizure frequency in existing studies

of treatment effectiveness. Working now to develop appropriate outcome measures for neurodevelopmental trajectories, functional performance, and quality of life for patients with early life epilepsies will be critical to the incorporation of nonseizure outcomes into future treatment trials.

This review underscores the need for high-quality investigations of early life epilepsy treatment. Given the difficulty in enrolling infants in RCTs, one pragmatic step would be to initiate a prospective multicenter observational registry measuring critical long-term outcomes such as neurodevelopment, functional performance, and quality of life. If sufficiently large, a registry would permit analyses specific to different etiologies, which may help targeted treatment choices to individual patients.

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Appendix Authors

Name	Location	Contribution
Jonathan R. Treadwell, PhD	ECRI-Penn Medicine Evidence-based Practice Center, ECRI, Plymouth Meeting, PA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Sudha Kilaru Kessler, MD, MSCE	Department of Pediatrics (Division of Neurology), Children's Hospital of Philadelphia; Departments of Neurology and Pediatrics, University of Pennsylvania Perelman School of Medicine	Drafting/revision of the article for content, including medical writing for content; study concept or design
Mingche Wu, MPH	ECRI-Penn Medicine Evidence-based Practice Center, ECRI, Plymouth Meeting, PA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Nicholas S. Abend, MD, MSCE	Department of Pediatrics (Division of Neurology), Children's Hospital of Philadelphia; Departments of Neurology and Pediatrics, University of Pennsylvania Perelman School of Medicine; Department of Anesthesia & Critical Care, University of Pennsylvania Perelman School of Medicine; Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania Perelman School of Medicine	Drafting/revision of the article for content, including medical writing for content; study concept or design
Shavonne L. Massey, MD, MSCE	Department of Pediatrics (Division of Neurology), Children's Hospital of Philadelphia; Departments of Neurology and Pediatrics, University of Pennsylvania Perelman School of Medicine	Drafting/revision of the article for content, including medical writing for content; study concept or design
Amy Y. Tsou, MD, MSc	ECRI-Penn Medicine Evidence-based Practice Center, ECRI, Plymouth Meeting, PA; Division of Neurology, Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia PA	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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