*Comparative Effectiveness Review Disposition of Comments Report*

**Research Review Title:** *Management of Infantile Epilepsies*

Draft report available for public comment from July 23, 2021, to September 6, 2021.

**Citation:** Treadwell JR, Wu M, Tsou AY. Management of Infantile Epilepsies. Comparative Effectiveness Review No. 252. (Prepared by the ECRI–Penn Medicine Evidence-based Practice Center under Contract No. 75Q80120D00002.) AHRQ Publication No. 22(23)-EHC004. Rockville, MD: Agency for Healthcare Research and Quality. PCORI Publication No. 2021-SR-01. October 2022. DOI: https://doi.org/10.23970/AHRQEPCCER252. Posted final reports are located on the Effective Health Care Program search page.

## Comments to Draft Report

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each draft report is posted to the EHC Program website or AHRQ website for public comment for a 3- to 4-week period. Comments can be submitted via the website, mail, or email. At the conclusion of the public comment period, authors use the commentators' comments to revise the draft report.

Comments on draft reports and the authors' responses to the comments are posted for public viewing on the website approximately 3 months after the final report is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

This document includes the responses by the authors of the report to comments that were submitted for this draft report. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

## Summary of Peer Reviewer Comments and Author Response

This research review underwent peer review before the draft report was posted for public comment on the EHC website. Reviewers generally agreed that the main contribution of the report will be to catalog the inadequacies of the current evidence, rather than giving clear answers to clinicians for helping manage today's infants with epilepsy. Specifically, the risk of bias of current studies and the fact that so few measure outcomes beyond seizure freedom and seizure frequency are important areas for future research. Peer reviewers expressed concerns about some aspects of the review, which are detailed next.

Some felt that our date cutoff (i.e., studies published in 1999 or later) may have excluded important older studies. We responded that, even though this may be true, later evidence is likely to capture most of the evidence, and we received input during protocol development that earlier studies were not likely to contribute substantially.

Reviewers questioned the inclusion of three studies: one of vigabatrin for infants with "epileptic spasms" (we still included it based on input from our subject matter experts because the study also said patients were having "seizures"), one of phenytoin because it was initially indicated for epileptic spasms (we still included it because the one study did enroll patients with seizures), and one of tumor resection (we still included it because it did meet our inclusion criteria and we sequestered its results from other studies).

Some reviewers felt our conclusions were worded too strongly in the face of Low strength of evidence (e.g., "cause" instead of "may cause"), and we softened the language accordingly. Others felt our conclusions about seizure freedom after surgery were not strong enough (we had rated the evidence as Low strength because of the high risk of bias, and we did not strengthen the wording). One wished we had attempted to quantify the size of the potential benefits (potentially via metaanalysis), but we felt the evidence quality was too low to warrant such analyses.

For surgery, reviewers suggested we attempt to stratify by etiology, distinguish between the planned and unplanned complications, and analyze hydrocephalus as an independent complication. For stratifying by etiology, we responded that this was not generally possible given the sparse reporting, but we did add a broad analysis specifically of hemimegalencephaly (HME) based on the reported individual patient data in eight surgical studies. We could not distinguish between the planned and unplanned complications because of poor reporting. For hydrocephalus, we revised the report accordingly and drew a new conclusion about it.

We made numerous terminology improvements based on reviewer suggestions (e.g., changing the title to infantile epilepsies to acknowledge the varying diagnoses, consistently stating 36 months rather than switching between 36 months and 3 years, updating language describing seizure types, and avoiding the broad term "hemispheric" when discussing surgical procedure). We also added more explanatory text based on reviewer input regarding (1) the roles of etiology, diagnosis, and genetic testing in guiding treatment choices, (2) surgery being used only after medications are unsuccessful, and (3) neuromodulation and gene therapy not being addressed in studies despite their being part of the scope.

*Source: https://effectivehealthcare.ahrq.gov/products/management-infantile-epilepsy/research*
*Published Online: October 25, 2022*

## Public Comments and Author Response

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **AANS-CNS** | General | This systematic review provides a comprehensive and exhaustive analysis of reported studies describing pharmacologic, dietary, and surgical treatments of infants (1 month < age < 36 months) with epilepsy, excluding those with West Syndrome or solely identified infantile spasms. The review exposes glaring inadequacies and evidence gaps in published data regarding the management of infants with epilepsy and represents an important contribution to the literature. Given the overall low or insufficient strength of evidence (SOE) for most outcomes assessed in the key questions (KQ), this systematic review has a lower magnitude of impact on guideline generation. However, this review contributes substantively to the academic pool of literature, highlighting the need for properly designed studies focusing on infants with epilepsy. The review provides important guidance on study components (e.g., seizure etiology, seizure type, prior interventions) to be considered and included for sufficient impact. | Thank you for your comment |
| **William Davis Gaillard, Children's National Hospital** | General | Overall a welcome document that is reasonably well done. The search is comprehensive and the selection criteria clear and rigorous. The challenging issue of surgical outcomes is fairly addressed. Typically, dietary therapy and certainly surgical therapy are only pursued when medical management has failed the child. For surgery, two appropriate medications in appropriate dosing must be used before surgery, in practice it is typically more, and current trends are to view as a treatment of choice and not last resort, but that is a separate issue. It is important to stress the need for other outcome measures beyond seizure control. | Thank you for your comments, yes in the Discussion under Evidence Gaps, we have stressed the importance of measuring outcomes such as hospitalization, neurodevelopment, infant quality of life, sleep outcomes, functional performance, and caregiver quality of life. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Ann Sodders, No affiliation listed** | General | The draft report in itself represents scientifically well the need for clinical practice guidelines, and patient centered outcomes. Professionally I worked clinically as an RN with the adult population. Personally, I care for an infant who was diagnosed with epilepsy at 9 months, and presently at 21 months the journey continues with intractable seizures, developmental delay, and an overwhelming feeling of questionable guidance from practitioners. Suggestions: Research needed to support clinical care and create clinical guidelines for all pediatric practices and specialties to access; a global data base for families/ care givers to enter information for researchers and clinicians to use-(We created our own excel tables with seizure logs including medications); round table discussions that include clinicians, experts, and lay people that are equally represented geographically and ethnically; shorten the clinical practice gap between patient/caregiver/ family and the physician- notably communication and care; clinical guidelines to use when research is not available. | Thanks for this comment and for sharing your experience. We agree that it is critical for future trials to improve measurement and reporting of outcomes and other measures to support future systematic reviews and ultimately facilitate development of evidence based clinical practice guidelines. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Mary Anne Meskis, Dravet Syndrome Foundation** | General | A major point that seems to be missing in the report is the push for genetic testing and diagnosis. There is so much variability on medications for each recognized disorder, and a proper diagnosis can really allow guidance on treatment. For instance, in Dravet syndrome (DS), in the list under Main Points Could there be a point made about the importance of early genetic testing and diagnosis to guide the management of infantile epilepsy within the report? There is so much variability for treatment within each developmental epileptic encephalopathy. An early diagnosis can appropriately guide treatment in a more systematic way. In addition, a full epilepsy genetic panel is now available through Invitae (Behind the Seizure) for patients 8 & under at no charge, removing financial barriers. For instance, in Dravet syndrome (DS), in the list of medications under Main Points (Levetiracetam may cause seizure freedom in some patients, but data on four other medications (topiramate, lamotrigine, phenytoin, vigabatrin): none of those are recommended first line treatments in DS; topiramate is a recommended second line treatment; levetiracetam is considered third line; and lamotrigine and phenytoin are contraindicated in care management for our community. | Since the report did not contain a Key Question or Contextual Question about genetic testing, it would not be appropriate to have a Main Point about it. We did look through our database and identified some studies of genetic testing and genome sequencing, and the discussion now contains the following test (with citations): "Some studies of genetic testing or genome sequencing of children with epilepsy has been conducted, and future work may elucidate whether such testing improves outcomes through the optimal selection of treatments." |
| **Mary Anne Meskis, Dravet Syndrome Foundation** | General | Perhaps it is too late to add anything in about early testing and diagnosis, but it feels like a missed opportunity and I do think it would add significant value. | Since the report did not contain a Key Question or Contextual Question about genetic testing, it would not be appropriate to have a Main Point about it. We did look through our database and identified some studies of genetic testing and genome sequencing, and the discussion now contains the following test (with citations): "Some studies of genetic testing or genome sequencing of children with epilepsy has been conducted, and future work may elucidate whether such testing improves outcomes through the optimal selection of treatments." |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **American Epilepsy Society (AES)** | Introduction | The authors note that genetics is playing an expanded role in the classification of infantile epilepsy but do not go into further detail. A more detailed discussion of genetics would enhance this review, although AES recognizes the limited information available from the primary literature. | Since the report did not contain a Key Question or Contextual Question about genetic testing, it would not be appropriate to have a Main Point about it. We did look through our database and identified some studies of genetic testing and genome sequencing, and the discussion now contains the following test (with citations): "Some studies of genetic testing or genome sequencing of children with epilepsy has been conducted, and future work may elucidate whether such testing improves outcomes through the optimal selection of treatments." |
| **AES** | Introduction | AES recognizes that exclusion of infantile spasms from the project scope enabled a much-needed focus on the infantile epilepsy evidence for this PCORI [funded] small systematic review. Providing more detailed rationale as part of discussion of other acknowledged limitations of the project, will allow clinicians in practice who treat infants across all epilepsy conditions to understand this scope decision. | We have added more justification for our exclusion of infantile spasms, along with 4 new citations of existing systematic reviews and guidelines, as well as the 2 new citations regarding infantile spasms during COVID-19. Please note that if infants in a study were all having both epileptic seizures and infantile spasms, it would not have been excluded for the infantile spasms component. We did require that at least 80% of infants not have only infantile spasms. Regarding the title itself making clear that the report does not address infants who only have infantile spasms, we considered changing it to "Management of Infantile Epilepsies That Are Not Exclusively Infantile Spasms", but to us this seemed too cumbersome. |
| **William Davis Gaillard, Children's National Hospital** | Introduction | You comment that treating seizures may cause adverse effects and harms that may also contribute to delayed development or reduced cognitive function. This is not well substantiated. Farwell demonstrated decreased IQ with PB (an earlier study; and resolved (in part) when dc'ed). Those of us who treat patients with epilepsy recognize that medication toxicity and encephalopathy happens, more with some meds than others, in general they are reversible and not permanent. There is concern, based on experimental animal studies, about some medications causing apoptosis which is viewed as not good for development but seizures are not good for brain cells either. I think this is a topic for further investigation and might be raised as a future need. | We changed "However, treating seizures may cause adverse effects and harms that may also contribute to delayed development or reduced cognitive function. " to "However, treatments for seizures may also cause short-term harms that can mean lower adherence or a suboptimal benefit-harm tradeoff." |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **M.A. Whelan, No affiliation listed** | Introduction | First, the review excludes a huge category of patients - those with Infantile Spasms, or West's syndrome. Accordingly, this limitation should be mentioned in the title which as it stands is somewhat misleading. | We have added more justification for our exclusion of infantile spasms, along with 4 new citations of existing systematic reviews and guidelines, as well as the 2 new citations regarding infantile spasms during COVID-19. Please note that if infants in a study were all having both epileptic seizures and infantile spasms, it would not have been excluded for the infantile spasms component. We did require that at least 80% of infants not have only infantile spasms. Regarding the title itself making clear that the report does not address infants who only have infantile spasms, we considered changing it to "Management of Infantile Epilepsies That Are Not Exclusively Infantile Spasms", but to us this seemed too cumbersome. |
| **M.A. Whelan, No affiliation listed** | Introduction | Second, the Structured Abstract comes too close to implying that seizure activity is a direct cause of the ASSOCIATED developmental problems, as on p. V11. Occasionally of course this may be the case - even with the exclusion of status epilepticus - but it needs to be acknowledged that more often the epileptiform activity is the epiphenomenon of clinical manifestation of brain abnormality underlying both seizures and developmental difficulties. | You refer to our sentence "Uncontrolled seizures in children 1 to 36 months old have serious short-term health risks and may lead to substantial developmental, behavioral and psychological impairments". We edited "may lead to" to "may be associated with", which clearly allows for additional causes, as you suggest |
| **M.A. Whelan, No affiliation listed** | Introduction | Fourth: on p. ES-1, last paragraph - what is meant by "pragmatic considerations and feasibility"? "Pragmatic considerations arising from "the limited nature of this review" (p. 2) is circular reasoning, not an explanation. | We changed "because of pragmatic considerations regarding feasibility" and "pragmatic considerations involving the limited nature of this review" to "resource constraints" |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **AES** | Methods | From the perspective of clinicians applying the review, the use of narrow criteria and the grouping together of various types and etiologies of infantile epilepsy may also be viewed as a limitation. Further explanation of the methodological rationale for these decisions would be helpful to enhance readers' understanding of the application and limits of evidence-based methodologies. | Thanks for this comment. Understandably, clinicians would prefer to have data for each seizure etiology and intervention. However, a majority of studies lumped outcomes of children with different etiologies together. The criteria for study inclusion were informed by our technical expert panel and were fairly inclusive-- we considered all study types and included studies with as few as 10 patients for surgical interventions. Given the sparse evidence base, we categorized surgical interventions into broader categories (with input from our TEP) to facilitate sufficient evidence to draw conclusions. Furthermore, this was designated a small AHRQ systematic review meaning the targeted number of studies for inclusion was ~40. Thus, for this project, given resource constraints including more studies would not have been feasible. We did provide an analysis by etiology for the surgical studies that reported individual patient data. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **AES** | Methods | The 1999 literature publication date cutoff limits the number of studies included in this review and misses trials with older antiseizure medications as well as key literature on surgical techniques that pre-dates 1999. Including papers on from 1980 forward will better reflect the evidence for surgeries such as anatomical hemispherectomies. | We completely understand your concern about our exclusion of any studies published in 1998 or earlier. In the planning stage, we considered with our technical expert panel (TEP) the idea of going back to 1990, but ultimately rejected the idea. This was because our TEP generally felt that 1999+ would represent the large bulk of the literature relevant to today's clinical practice, and also that the report was designated as a "small" systematic review by AHRQ. We also knew that we would be ordering full text for many articles whose abstracts were unclear about they reported any data for age 1-36 months, and the necessary time to sift through those full articles meant we would likely not have enough time to screen the number of studies that using 1990+ would have yielded. We have added discussion of this review limitation in the Discussion, acknowledging that evidence on some older medications and surgical procedures was likely omitted from the report for this reason, and that the lack of evidence on a given treatment in this report does not mean that the treatment should not still be considered by clinicians in their efforts to tailor treatments to patients. We included four studies of topiramate and one study of phenytoin. Regarding carbamazepine, we did include one study that compared it to topiramate. We agree that the timing of 1999+ likely was fortuitous for levetiracetam, given its FDA clearance in late 1999. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **AES** | Methods | Both the inclusion requirement that at least 80% of a study population must be 36 months of age or younger, and the minimum sample size of 30, may have resulted in omission of some key studies from the review. The minimum sample size of 10 per procedure for surgical studies, however, is appropriate. More robust discussion of the rationale for these inclusion/exclusion criteria would be helpful. | We added a new paragraph in the discussion about our inclusion criteria. "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 ≥ 10 for RCTs, n ≥ 10 for non-randomized studies of surgery, and n ≥ 30 for non-randomized studies of medications or diets). As many have noted this age group is clinically distinctive from both neonates and older children 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) as only 68% of patients were age 1-36 months). " |
| **AES** | Methods | The stringent inclusion/exclusion criteria may also explain why some reports on recent surgical technique like laser interstitial thermal therapy (LITT) in children less than 36 months are excluded. Obviously a metanalysis will have summated disparate studies, but in an effectiveness report such as this that is not designed to do so, close consideration of the impact of exclusion criteria is particularly important. For example, data from the only randomized controlled trial of epilepsy surgery versus medical therapy in pediatric patients were excluded on the basis that at least 80% of the subjects were not less than 36 months old. (Dwivedi R, Ramanujam B, Chandra PS, et al. Surgery for Drug-Resistant Epilepsy in Children. N Engl J Med. 2017;377(17):1639-1647. doi:10.1056/NEJMoa1615335. PMID 29069568.) | We added a new paragraph in the discussion about our inclusion criteria. The study you cite reported median ages of 9 or 10 years old, which seems too different developmentally to be considered relevant to this report. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **William Davis Gaillard, Children's National Hospital** | Methods | There are important and classic older papers, especially for epilepsy surgery in the early 90s will be from Miami group, maybe Cleveland Clinic. Same is true for the older anti-seizure medications VPA and CBZ though I am not sure change findings. Furthermore, the recent cross sectional European collaborative outcomes study on several hundred patients will include a substantial number of children < 36 mo who had surgery, one could ask for this subgroup data. | We completely understand your concern about our exclusion of any studies published in 1998 or earlier. In the planning stage, we considered with our TEP the idea of going back to 1990, but ultimately rejected the idea. This was because our TEP generally felt that 1999+ would represent the large bulk of the literature relevant to today's clinical practice, and also that the report was designated as a "small" systematic review by AHRQ. We also knew that we would be ordering full text for many articles whose abstracts were unclear about they reported any data for age 1-36 months, and the necessary time to sift through those full articles meant we would likely not have enough time to screen the number of studies that using 1990+ would have yielded. We have added discussion of this review limitation in the Discussion, acknowledging that evidence on some older medications and surgical procedures was likely omitted from the report for this reason, and that the lack of evidence on a given treatment in this report does not mean that the treatment should not still be considered by clinicians in their efforts to tailor treatments to patients. We included four studies of topiramate and one study of phenytoin. Regarding carbamazepine, we did include one study that compared it to topiramate. We agree that the timing of 1999+ likely was fortuitous for levetiracetam, given its FDA clearance in late 1999. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Emily Spelbrink, Pediatric Epilepsy Research Consortium Early Life Epilepsies Special Interest Group** | Methods | In the title and earlier in the text, it needs to be clear that infantile spasms are excluded, and the justification for doing this. However, the authors acknowledge later in Applicability that children with epileptic spasms were included in some of the studies, so it is unclear if this is actually the case, and should be clearly stated as a limitation. This relates also to the next point about different mechanisms and mixing in more refractory epilepsies masking effects, and should be clearly acknowledged; perhaps “Infantile spasms are excluded to the extent possible given conflicting terminology.” | We have added more justification for our exclusion of infantile spasms, along with 4 new citations of existing systematic reviews and guidelines, as well as the 2 new citations regarding infantile spasms during COVID-19. Please note that if infants in a study were all having both epileptic seizures and infantile spasms, it would not have been excluded for the infantile spasms component. We did require that at least 80% of infants not have only infantile spasms. Regarding the title itself making clear that the report does not address infants who only have infantile spasms, we considered changing it to "Management of Infantile Epilepsies That Are Not Exclusively Infantile Spasms", but to us this seemed too cumbersome. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Moshe, Albert Einstein College of Medicine** | Methods | My concern is the time of the survey: January 1, 1999 to November 30, 2020. During this time is highly unlikely there will be many papers touting phenytoin (especially) and may be topiramate. There is no mention of carbamazepine. Since levetiracetam became available around 2000, it is more likely that there will be articles touting its efficiency. | We completely understand your concern about our exclusion of any studies published in 1998 or earlier. In the planning stage, we considered with our TEP the idea of going back to 1990, but ultimately rejected the idea. This was because our TEP generally felt that 1999+ would represent the large bulk of the literature relevant to today's clinical practice, and also that the report was designated as a "small" systematic review by AHRQ. We also knew that we would be ordering full text for many articles whose abstracts were unclear about they reported any data for age 1-36 months, and the necessary time to sift through those full articles meant we would likely not have enough time to screen the number of studies that using 1990+ would have yielded. We have added discussion of this review limitation in the Discussion, acknowledging that evidence on some older medications and surgical procedures was likely omitted from the report for this reason, and that the lack of evidence on a given treatment in this report does not mean that the treatment should not still be considered by clinicians in their efforts to tailor treatments to patients. We included four studies of topiramate and one study of phenytoin. Regarding carbamazepine, we did include one study that compared it to topiramate. We agree that the timing of 1999+ likely was fortuitous for levetiracetam, given its FDA clearance in late 1999. |
| **Ann Sodders, No affiliation listed** | Methods | In regards to medications, what about other medications used for epilepsy in this population? | A list of all medications considered appears in the appendix. We note in the Discussion any oft-prescribed medications for which we included no evidence, such as oxcarbazepine. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **M.A. Whelan, No affiliation listed** | Methods | More seriously perhaps, and As a function of this, it excludes any mention of the drug of sodium valproate. Even allowing for the problem of the use of this drug under the age of 2 - namely, an increase risk of serious and potentially fatal adverse reactions - it also has excluded a review of the use of this valuable anticonvulsant drug between the ages of two and three. It is also of course used in children under the age of 2, at the discretion of the provider. Even if adequate studies are lacking per your criteria, it still should be referenced. | We did not exclude any mention of valproate. One included RCT compared valproate alone to valproate+levetiracetam, and we discussed that study at length. Since this was the only study using valproate, we discussed the results within the levetiracetam section. The revision adds mention of valproate and that its results are discussed in the levetiracetam section. |
| **M.A. Whelan, No affiliation listed** | Methods | Third there is no discussion of, or reference to, the etiology of the seizure activity as pertinent to the choice of anticonvulsants. There is brief acknowledgement of the pertinence of genetic testing but as there may be a direct relationship between mitochondrial dysfunction or other genetic aberrations and anticonvulsant choice, this needs further discussion and at least acknowledgement. Excluding "metabolic epilepsies" (Table, p. 6) is problematic. | The revision provides more text on etiology as well as genetic causes. We excluded metabolic epilepsies due to different biology and treatments based on the advice of our subject matter experts, and with no disagreement from our Technical Expert Panel. |
| **AES** | Results | The term “brain stimulation” is used in the report and is limiting. AES suggests that a better term is “neuromodulation” which includes techniques like vagus nerve stimulation which involves peripheral or cranial nerve stimulation in addition to brain stimulation techniques. | We changed "brain stimulation" to "neuromodulation " |
| **AES** | Results | A paper on a multicenter study of epilepsy surgery in children less than 3 months old has recently been published and should be included when final literature updates are made. Recognizing that this study was very recently published after the initial literature searches for this review, AES notes that it is very relevant and is likely to be cited significantly in the near future. (Roth J, Constantini S, Ekstein M, et al. Epilepsy surgery in infants up to 3 months of age: Safety, feasibility, and outcomes: A multicenter, multinational study. Epilepsia. 2021;62(8):1897-1906. doi:10.1111/epi.16959. PMID 3412854) | Thank you for this comment. This study (Roth et al.) was included in the revised report. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **AES** | Results | As expected, this report exposes the known paucity of high quality studies on the efficacy of epilepsy surgery techniques in children, because children are often not included in trials of epilepsy surgery techniques. AES applauds the fact that this rigorous systematic review highlights this paucity of relevant studies. The review has great potential to spur future well-designed studies to fill gaps in evidence to support optimal clinical care. | Thank you for your comment |
| **AANS-CNS** | Results | Overall, there do not appear to be any major shortcomings or problems with this systematic review related to pediatric neurosurgery. However, the subdivisions of studies regarding surgical therapy are not as clearly demarcated outside of anatomic hemispherectomy and functional hemispherotomy, which may represent a minor issue or concern. The authors combine various types of surgical resection or disconnection (frontal or temporal, intra-lobar, multi-lobar, focal cortical resection, posterior disconnection) into a single category designated as 'non-hemispheric' procedures. While this may be dictated by the scarcity of published studies, this crude grouping scheme under-appreciates and over-simplifies the complexity of different pathologies (focal cortical dysplasia, more diffuse cortical dysplasia, polymicrogyria, cortical tubers, encephalomalacia, etc.) and neuroanatomic locations of epileptogenicity that may impact outcomes. Ideally, the various types of surgeries and/or neuroanatomic locations of resection would be separated. Unfortunately, this may be limited by the availability of reported studies fulfilling inclusion criteria. | We agree that ideally, studies of surgical interventions would offer more details regarding surgeries such as the commenter suggests. However, many surgical studies reported only overall summary data for different types of procedures or provided details for procedures (for example % of right and left procedures/extent of resections) but only reported outcomes for "focal surgery" vs. "hemispheric surgery". Because data were reported in this way for so many studies we were unable to provide more nuance regarding outcomes. We have added the following text in the Discussion to highlight this point "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 synthesizing or pooling data across studies. " |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **William Davis Gaillard, Children's National Hospital** | Results | OXC is the most commonly used medication in this age group (Whilmhurst et al), rather than LVT though LVT used more commonly in USA. Agree it is surprising there are no data on this medication, but this is common for first line medications. Not including older literature may miss Carbamazepine (CBZ). It is odd that there are data for PO DPH; it is not surprising efficacy is poor as DPH is not well absorbed in the guts of infants and toddlers, this is a well known observation and PO DPH should not be used in this population (IV for acute seizures is a different issue). | The revision now states "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", and also acknowledges that our cutoff of 1999 would like miss studies of older medications such as carbamazepine. We are not sure what you mean by "PO DPH"; DPH could mean diphenylhydantoin, which was not on our list of included medications. If you meant phenytoin, yes this is used intravenously for acute seizures, but in the included study, it had been used orally in other patients for seizure prophylaxis (which the review clarifies). |
| **William Davis Gaillard, Children's National Hospital** | Results | It is stated there are no PB studies but there is with the Grinspan study that is discussed. I suspect the VGV studies are for IS and in TSC patients, these data need to be reexamined in this light and likely excluded (as epileptic spasms =infantile spasms). There is a distinction between an adverse event on a medication vs. ill effects or side effects that should be clarified. Infection risk presented derives from underlying disease, or sedation; there is risk of infection with immune suppression but you did not review everolemus trials in TSC. | Yes, Grinspan did have a phenobarbital group, so we corrected our prior assertion that there was no evidence on PB. For vigabatrin, we included one study, and patients had "epileptic spasms" as well as "seizures". Given the uncertainty in terminology, we chose to include it, after consultation with our subject matter experts. We are unfamiliar with the distinction you mention between an adverse effect and a side effect, and we suspect that the subtlety of that distinction is not important enough to warrant mention. It is true that we included no trials of everolemus. |
| **William Davis Gaillard, Children's National Hospital** | Results | The dietary articles should be analyzed by intention to treat, not those who do well who remain on the diet. The randomized controlled infant keto diet study closed this month with data analysis. Dietary therapy has its own set of risks, not stated. | We agree about intention to treat, and where possible based on study reporting, we provided the data in that way. We look forward to seeing the results of the RCT you mention. For dietary risks, we re-examined the diet studies for possible reporting of harms, and found a total of four studies which are now summarized in Key Question 3. |
| **William Davis Gaillard, Children's National Hospital** | Results | I would not say surgery causes seizure freedom, cause is usually used as etiology of disease, I think results or contributes or associated a better term. As for semantics it should be surgery not surgeries (a common misuse). | We prefer "causes", since KQs 1 and 2 referred to "effectiveness" (i.e., cause), and we assessed the risk of bias of studies in that context, we believe that cause is the best choice of word. Note that we were discussing what causes outcomes, not what causes epilepsy in the first place. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **William Davis Gaillard, Children's National Hospital** | Results | While this is a welcome rare review that critically assesses surgery as a treatment option I am not sure there is appropriate consideration given to surgical approaches, they are both lumped and then statements made that different approaches that can't be disentangled. It is fair to break down to focal resection and hemispherectomy (and here there are two approaches functional less likely to succeed but fewer complications e.g. shunt). The other distinction is by pathology, and that could be at least discussed; but the big distinction is lesion vs no lesion. Perhaps this is a topic for further study (which larger populations) | Thanks for this comment. Unfortunately, enough studies of surgery did not report enough details to allow for us to categorize outcomes by pathology. We agree that this would be helpful. If future studies included pathology/seizure etiology not only in the description of included patients, but reported outcomes by pathology/etiology this would support this type of analysis in future systematic reviews. We did provide an analysis by etiology for the surgical studies that reported individual patient data. |
| **William Davis Gaillard, Children's National Hospital** | Results | Stating some may improve with surgery I think a bit understated. There is a problem with the Boston study that needs to be critically considered. (and there are reasons for surgery failure). Admittedly open unblinded self assessment is 70-85% seizure free when in reality likely closer to 50% longer term, yet this remains better than 3-10% for medication number 3 (if you extrapolate from studies in older epilepsy populations and the observation the infantile epilepsies can be nasty to treat). It is appropriate and important to review and comment on risk of surgery. Surgery is elective, bleeding infection, stroke, hydrocephalus and death occur. I think you will find hemispherectomy deaths occurring in 1980s and maybe early 90s, but with techniques established, death is now rare for hemispherectomy let alone focal resection. The surgical death you report in a TSC tumor surgery is NOT death from epilepsy surgery and should be removed. There are risks in those < 3 months and 5 kg so surgeons are reluctant to operate on this group. The risks of focal resection are < than hemispherectomy, and that does not come across. To be balanced one also needs to include risks of untreated refractory epilepsy which is 1/100 years for SUDEP alone so the cumulative mortality is high (Sillanpaa/the Camfields) in this population. There is an odd comment that one can't comment on seizure reduction for some epilepsy studies, but achieving seizure freedom is a (the best) form of seizure reduction. You state most infants had surgery for intractable epilepsy, the statement here should be all. Tumor surgery is different, it is not epilepsy surgery | Thanks for this comment. The wording of the conclusion statement "Some infants with medically refractory epilepsy achieve seizure freedom after hemispherectomy/hemispherotomy" is intended to reflect the fact that the evidence base is too sparse to support a more precise estimate of how many or which infants achieve seizure freedom after this particular procedure. Regarding the comment "There is a problem with the Boston study that needs to be critically considered." we are unaware of what problem the commenter is referring to and so are unable to address this. Regarding the mortality after surgery, our protocol specified inclusion of any mortality, so we describe the mortality as reported by study authors. More importantly, we understand the concern that for infants undergoing surgery, the range of outcomes reported compare favorably to accepted outcomes for infants receiving a 3rd antiseizure medication. However, as no studies directly compared these two treatment options, the systematic review does not address this. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **William Davis Gaillard, Children's National Hospital** | Results | It may be helpful to state why some data are not available. For example, the first gene therapies for (infantile) epilepsy began this year, so they will be coming down the pike. There are technical limitations to surgical stimulation approaches. It should also be recognized these are palliative and not curative approaches. There are some VNS placed in children < 3 years but uncommon for technical reasons (e.g. size of battery/generator relative to size of child). There is no FDA approval for DBS or RNS in this age group and there are technical considerations that preclude these approaches. It is also likely fair to state that there are likely different genetic epilepsy not distinguished in the studies reviewed. | We added "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 EU orphan drug status in August of 2021; clinicaltrials.gov lists a trial begun in March of 2021 (https://clinicaltrials.gov/ct2/show/NCT04798235).. " We do understand that many therapies, particularly pharmacological and dietary therapies, are palliative rather than curative. Regarding different genetic epilepsies, the revision acknowledges this more fully. |
| **Emily Spelbrink, Pediatric Epilepsy Research Consortium Early Life Epilepsies Special Interest Group** | Results | The evidence that exists about treatments and their effectiveness in this age group is more than represented here, in that evidence based medicine has progressively sought to target epilepsies per their etiologies/mechanisms (which would have <30 infants per group). Additionally, lumping treatment outcomes for different etiologies and refractory and nonrefractory epilepsies (and even tumors – comment is made about staging, but not about whether resection was believed full vs palliative?) will likely dilute effects that could be seen in these respectively. More prominent acknowledgement of this in the abstract or highlighted text would be helpful. Additionally, if this review led the authors to wish for more larger studies with certain parameters, or if they would suggest a parallel review/meta-analysis to this for smaller (n<30 or 10) ELE studies, including these explicitly in the discussion would help direct future work. | Thanks for this comment. Most children receiving dietary or surgical interventions had refractory epilepsy. We included 1 study describing infants undergoing surgery for epilepsy due to malignancy. However, in recognition of the fact that these patients differ clinically, the study is presented in its own section and does not contribute to the evidence base for any conclusions. |
| **Emily Spelbrink, Pediatric Epilepsy Research Consortium Early Life Epilepsies Special Interest Group** | Results | Maximum follow up duration for harms evidence need to be highlighted as important, in addition to minimum follow up duration of zero. Many of our parents really want to know if their child will have intellectual or functional deficits when they're 5 after taking a drug as an infant. This data is almost certainly insufficient, but will be important for future studies as possible. | We have added to the discussion under harms: "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. Many parents are anxious to know about these long-term harms, particularly regarding neurocognitive development, so long-term studies are particularly important for future work." |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Philip Pearl, Children's Hospital Boston** | Results | The report does not take into consideration the publication by the Child Neurology Society and the Pediatric Epilepsy Research Foundation on the standard of care for the evaluation and management of infantile spasms during the time of a pandemic. This has changed clinical practice and it is an oversight to not have cited and explained the changes, which emphasize less reliance on inpatient video-EEG studies and IM ACTH. References: 1.Management of Infantile Spasms During the COVID-19 Pandemic. Grinspan ZM, Mytinger JR, Baumer FM, Ciliberto MA, Cohen BH, Dlugos DJ, Harini C, Hussain SA, Joshi SM, Keator CG, Knupp KG, McGoldrick PE, Nickels KC, Park JT, Pasupuleti A, Patel AD, Shahid AM, Shellhaas RA, Shrey DW, Singh RK, Wolf SM, Yozawitz EG, Yuskaitis CJ, Waugh JL, Pearl PL. J Child Neurol. 2020 Oct;35(12):828-834. doi: 10.1177/0883073820933739. Epub 2020 Jun 23. PMID: 32576057 2. Crisis Standard of Care: Management of Infantile Spasms during COVID-19. Grinspan ZM, Mytinger JR, Baumer FM, Ciliberto MA, Cohen BH, Dlugos DJ, Harini C, Hussain SA, Joshi SM, Keator CG, Knupp KG, McGoldrick PE, Nickels KC, Park JT, Pasupuleti A, Patel AD, Pomeroy SL, Shahid AM, Shellhaas RA, Shrey DW, Singh RK, Wolf SM, Yozawitz EG, Yuskaitis CJ, Waugh JL, Pearl PL; Child Neurology Society (Practice Committee and Executive Board) and the Pediatric Epilepsy Research Consortium (Infantile Spasms Special Interest Group and Steering Committee). Ann Neurol. 2020 Aug;88(2):215-217. doi: 10.1002/ana.25792. Epub 2020 Jun 8. | We have added more justification for our exclusion of infantile spasms, along with 4 new citations of existing systematic reviews and guidelines, as well as the 2 new citations regarding infantile spasms during COVID-19. Please note that if infants in a study were all having both epileptic seizures and infantile spasms, it would not have been excluded for the infantile spasms component. We did require that at least 80% of infants not have only infantile spasms. Regarding the title itself making clear that the report does not address infants who only have infantile spasms, we considered changing it to "Management of Infantile Epilepsies That Are Not Exclusively Infantile Spasms", but to us this seemed too cumbersome. The studies that you cite were all about infantile spasms, thus they were excluded. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Philip Pearl, Children's Hospital Boston** | Results | The results and conclusions do not represent current practice and recommendations without taking into account the references noted above. | We have added more justification for our exclusion of infantile spasms, along with 4 new citations of existing systematic reviews and guidelines, as well as the 2 new citations regarding infantile spasms during COVID-19. Please note that if infants in a study were all having both epileptic seizures and infantile spasms, it would not have been excluded for the infantile spasms component. We did require that at least 80% of infants not have only infantile spasms. Regarding the title itself making clear that the report does not address infants who only have infantile spasms, we considered changing it to "Management of Infantile Epilepsies That Are Not Exclusively Infantile Spasms", but to us this seemed too cumbersome. |
| **M.A. Whelan, No affiliation listed** | Results | Fifth: What is meant by "prior medication" (p. 43) as a source of visual difficulties? This needs explanation and defense. Also, the impression is left that all problems related to Vigabatrin use are self-resolving after medication discontinuation. Documentation? | The authors of the vigabatrin study stated that the pre-vigabatrin eye exam revealed eye abnormalities in 34/49 patients, which were said by the authors to be "due to TSC, an underlying disease, refractive errors, medication, and unknown reasons". Authors did not state specifically which baseline medication(s) had caused these eye abnormalities; a total of 17 medications that were being used by study patients. For the revision, we added that "The study did not report which baseline medications were likely responsible for the pre-vigabatrin abnormal eye exam results". Regarding the resolution of eye problems, we had not meant to imply that ALL harms of vigabatrin are self-resolving after discontinuation. We wrote "some evidence suggests that vigabatrin may cause temporary vision abnormalities, but only a single pre/post study has addressed the issue", which was only about vision, not all possible harms. |
| **AES** | Discussion | AES recommends that the Limitations section be expanded to reflect the above comments and that robust explanations of rationale for inclusion/exclusion criteria and other methodological decisions be included. | We added a new paragraph in the discussion about our inclusion criteria. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **AES** | Discussion | The impact of this review would also be enhanced by a discussion of information or lack thereof on health disparities and non-modifiable patient factors (gender, race, ethnicity, socioeconomic, and demographic factors), similar to the discussion addressing the relative paucity of quality of life data in the studies reviewed. | None of Key Questions or Contextual Questions involved these factors. We do mention economic hardship in the Discussion. |
| **AES** | Discussion | AES views this review as an opportunity to highlight future research needs in all areas where the epilepsy community lacks robust data to advance clinical care of people with epilepsy. | We agree, thank you |
| **AES** | Discussion | Finally, AES recommends the inclusion in final literature updates of newer studies missed in this review. (e.g., Mann D, Antinew J, Knapp L, et al. Pregabalin adjunctive therapy for focal onset seizures in children 1 month to <4 years of age: A double-blind, placebo-controlled, video-electroencephalographic trial. Epilepsia. 2020;61(4):617-626. doi:10.1111/epi.16466. PMID 32189338; and Roth et al. as cited previously) | The Mann study did not meet our inclusion criteria because <80% were age 1-36 months at the time of treatment |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **AES** | Discussion | Suggestions for future reviews or updates of the current review include a focus on newer treatments not well covered by this review (e.g., laser interstitial thermal therapy and gene therapy), and consideration of stratifying the infantile epilepsy patient population by genetic factors, which can greatly influence response to medication or dietary therapy and considerations for surgical planning. | Thank you for this comment, AHRQ may consider genetic testing for future reports. We did look through our database and identified some studies of genetic testing and genome sequencing, and the discussion now contains the following test (with citations): "Some studies of genetic testing or genome sequencing of children with epilepsy has been conducted, and future work may elucidate whether such testing improves outcomes through the optimal selection of treatments." We agree that it could be useful for future systematic reviews or updates of this review to address genetic testing or stratify results according to genetic etiology. We added the following text to the discussion to acknowledge this point "Some studies of genetic testing or genome sequencing of children with epilepsy has been conducted, and future work may elucidate whether such testing improves outcomes through the optimal selection of treatments." We also note that at present, most studies we identified did not report outcomes by genetic etiology. This would be an important first step to make it feasible for future systematic reviews to provide this type of analysis. |
| **William Davis Gaillard, Children's National Hospital** | Discussion | The call further study is important but there are constraints. As noted above dietary and surgical therapy are used after medications have failed and three studies show surgery superior to medical therapy when conditions to consider medical therapy, at least in older populations. Not that surgery is without risk, but those risks are up front and in long run better than risk of SUDEP or accidental death (not really discussed, e.g. the risk of not following aggressive Rx). One might conduct a study of surgery vs 3rd med, but this may be ethically dubious. One could study Keto diet vs a second or 3rd med. Also comment is made in the report about placebo arms which is ethically unacceptable; batter to randomize among meds for ne onset epilepsy. Comparative effectiveness studies as outlined for surgery are likely mor practicable. | Thanks for this comment. We understand and agree that in some contexts a placebo/sham arm would be considered unethical and comparative effectiveness trials may be a better trial design. We have added the following sentence to the discussion "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. " |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Emily Spelbrink, Pediatric Epilepsy Research Consortium Early Life Epilepsies Special Interest Group** | Discussion | Having reviewed existing literature extensively, and commented that it is difficult to compare different studies' data given different metrics, it would be helpful if this review could suggest the most useful metrics that have been used, and propose development of commonly useful metrics for the other parameters it seeks to promote study of, e.g., quality of life, sleep, development. Ideally metrics should reflect desired nuance if possible (e.g., sleep concerns are likely not adequately captured as "total time asleep at night" alone). Additionally, metrics that are believed important (e.g., baseline seizure frequency, as measure of disease severity, mentioned in Applicability; nonsyndromic epilepsy as a qualifier, mentioned in detail about Dr Grinspan's study) should be highlighted as important to include in future studies. As a possible model/analogy, recommendations for metrics and study design (see comment 5 below) have been published for neonatal seizures (e.g., Soul JS et al, PMID: 30584262). | Thanks for this comment. During the protocol development process, our key informants and technical expert panel identified many key outcomes. We have drawn attention to these by editing the following paragraphs in the discussion to include this information:<br>"Perhaps a more feasible next step for future trials would be designing a prospective multicenter observational cohort study. Such data could be captured by creation of 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: first, 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 regarding measurement of 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 synthesizing or pooling data across studies. " |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Emily Spelbrink, Pediatric Epilepsy Research Consortium Early Life Epilepsies Special Interest Group** | Discussion | A thoughtful recommendation about what study design/evidence the authors would consider adequate science, and also ethical given their results, would help guide future study design. This is a difficult problem and will continue to plague future study. Comments on this are presently buried in a sentence under Research and Health Policy section. The authors state strongly that “without randomization, inferring efficacy for drugs, dietary, and surgical therapies is likely to remain challenging given the number of concomitant therapies patients receive.” There is a brief mention of a withdrawal RCT as one option, but it is unclear if even that would be ethical for, for instance, surgical vs nonsurgical comparisons, and this is likely to be a concern with targeted genetic therapies and other rationally directed interventions. If the goal is finding the best care for patients as quickly as possible and within ethical parameters, there is very likely a role for smaller studies, and etiology-specific studies and even observational data for rare diseases, that should at least be mentioned for this age group. | Thanks for this comment. We agree that observational studies would represent an important next step. We had already noted that "more feasible next steps might include prospectively collected registry data with standardized measures" but to clarify this further we have added the following language to the discussion: "Perhaps a more feasible next step for future trials would be designing a prospective multicenter observational cohort study. Such data could be captured by creation of 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: first, given the relatively small number of infants undergoing surgical interventions, gathering data across multiple centers would offer important improvements to detect efficacy and harms;<br>2) such a registry could facilitate consensus regarding measurement of outcomes and<br>3) provide a framework for prospectively collecting data. Existing consortiums could play a role in facilitating development. |
| **Gary Matthern, UCLA** | Discussion | Should the report comment on when parents should seek higher level of care? once a child has failed two ASDs then should't they be referred to specialist. That is NOT clearly stated in the Summary. This is important as unless parents take control of the situation many children do not get the level of care needed. | We agree that parents would appreciate this guidance. However, EPC reports are not intended to assert when any clinical action "should" be undertaken. Instead, EPC reports are intended to provide the best synthesis of existing available evidence. A clinical practice guideline, for which this report may serve as the basis, would be the best place for such recommendations. |

| Commentator & Affiliation | Section | Comment | Response |
|---|---|---|---|
| **Gary Matthern, UCLA** | Discussion | A statement on neuroimaging. As shown in the study by Berg et al 2009 (Brain) best estimates is that MRI will find some lesion on the scan referable to the seizures in about 20% of cases and that lesion might be a surgical target in from 1 in 4 to 1 in 5 of those positive cases. Hence, it seems reasonable to recommend a good quality MRI in a child who is still having seizures after a trial of an ASD. That scan should probably be on at least a 3T scanner and read by a radiologist familiar with developmental brain disorders and epilepsy. Furthermore, a positive MRI scan was highly predictive of not being successfully controlled by ASDs in the Berg study and might prompt a referral to a comprehensive center for children. | We understand the potential importance of neuroimaging to guide treatment decisions; however, this report focuses on describing the outcomes of treatments in existing trials. |
| **Gary Matthern, UCLA** | Discussion | Statement on need to refer to specialty center when initial drugs fail. | We agree that parents would appreciate this guidance. However, EPC reports are not intended to assert when any clinical action "should" be undertaken. Instead, EPC reports are intended to provide the best synthesis of existing available evidence. A clinical practice guideline, for which this report may serve as the basis, would be the best place for such recommendations. |
| **Gary Matthern, UCLA** | Discussion | Discuss need for prompt neuroimaging as standard of care | We understand the possible importance of neuroimaging to guide treatment decisions, but this report focuses only the outcomes of treatments. |