Comparative Effectiveness Review
Number 252

Management of Infantile Epilepsies

Executive Summary

Main Points

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

Background and Purpose

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

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

Agency for Healthcare Research and Quality

Methods

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

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

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

Results

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

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

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

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

Twelve studies of pharmacologic interventions, four studies of dietary treatments, and 12 studies of surgery met inclusion criteria for our examination of treatment harms. Only pharmacotherapy studies collected and reported harms systematically. We concluded that for three medications (levetiracetam, topiramate, and lamotrigine) adverse effects are rarely severe enough to warrant discontinuing medication (SOE: Moderate for topiramate, and Low for the other two). For topiramate, we found consistent evidence of dose-response effects for two non-severe adverse effects (SOE: Moderate): loss of appetite and upper respiratory tract infection. For dietary treatments, evidence on adverse effects was insufficient to permit conclusions. For surgical interventions, based on eight studies after functional hemispherectomy/hemispherotomy and 4 studies of other non-hemispheric resective procedures (such as multilobar, lobar, or focal resections) we concluded that mortality after these procedures is rare (SOE: low).

Strengths and Limitations

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

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

Implications and Conclusions

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

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

Full Report

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