REVIEW ARTICLE

Advanced Treatments for Childhood Epilepsy

Beyond Antiseizure Medications

Sucheta M. Joshi, MD, MS; Rani K. Singh, MD; Renée A. Shellhaas, MD, MS

A substantial minority of children with epilepsy have continued seizures despite adequate trials of standard antiseizure medications. To maximize seizure control and thereby optimize their neurodevelopmental outcomes, alternate nonmedication therapies should be considered for these patients. Dietary therapies, including the ketogenic diet and its variations, have been available for years. With a recent resurgence in popularity and expansion of indications, these treatments can lead to freedom from seizures or a significantly reduced seizure burden for a large number of patients. For carefully selected individuals, resective epilepsy surgery may offer the best hope for a cure. For others, palliation may be achieved through additional surgical approaches, such as corpus callosotomy and multiple subpial transections, or through neurostimulation techniques, such as the vagus nerve stimulator. In this review, we present these nonmedication approaches to treatment-resistant childhood epilepsy, with attention to patient selection and the potential risks and benefits. *JAMA Pediatr. 2013;167(1):76-83. Published online November 12, 2012. doi:10.1001/jamapediatrics.2013.424*

Nearly 1% of children in the United States have epilepsy.[1] Controlling seizures in these children offers the best opportunity to maximize their neurodevelopmental potential and quality of life. For about 70% of children, seizures respond fully to antiseizure drugs. However, medications fail to control the seizures for a substantial minority of children with epilepsy. Kwan and Brodie[2] showed that 47% of patients with epilepsy (ages 9-93 years) became seizure free with their first medication, whereas the second and third drugs resulted in freedom from seizures among only 14% and 4%, respectively. The International League Against Epilepsy now defines treatment resistance as epilepsy with seizures that are not controlled despite adequate trials of 2 appropriately chosen and well-tolerated antiseizure drugs.[3] Among children with treatment-resistant epilepsy, alternatives to medical treatment should be considered because alternative treatment may offer the best chance for seizure control and can often improve cognition and quality of life. Herein, we review these treatment options, including dietary therapies, epilepsy surgery, and neurostimulation.

Author Affiliations: Division of Pediatric Neurology, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor.

DIETARY THERAPIES

Fasting has long been known to be effective in treating seizures, as described by Hippocrates and the New Testament's Gospel of Mark.[4] With the discovery of ketones (acetone and β-hydroxybutyrate) in patients who were fasting or eating a diet with high levels of fat and inadequate carbohydrates, the ketogenic diet was conceived.[4] Pioneered by Wilder in 1921,[5] the ketogenic diet became a relatively popular treatment for epilepsy until the advent of phenytoin sodium (introduced in 1938) and the subsequent era of antiseizure medications. For the next 60 years, use of the ketogenic diet declined progressively. However, since the late 1990s, clinical and research interest in dietary treatments for epilepsy have revived. At present,

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archpedi.jamanetwork.com/ on 05/06/2015

several dietary therapies are available for patients with treatment-resistant epilepsy.

The classic ketogenic diet is calculated based on the ratio of fat to protein and carbohydrates. Typically a 3:1 or 4:1 ratio is administered. The fats are usually long-chain triglycerides, and only the minimum amount of protein required for physical growth is provided. Parents must meticulously calculate and weigh each food and beverage; even a small error can result in inefficacy. Still, many patients experience significant improvement in seizure burden and in cognition.

Because the classic ketogenic diet is so strict and is unpalatable to some children, modifications have been innovated. Medium-chain triglyceride (MCT) oils provide more ketones per kilocalorie than long-chain triglycerides, so less fat is required in the MCT diet than the classic ketogenic diet. This modification leads to increased flexibility with protein and carbohydrate content and can improve palatability, although adverse gastrointestinal tract effects can be problematic.

The modified Atkins (MA) diet, based on the widely used weight-loss regimen, has gained in popularity among older children, adolescents, and most recently adults with epilepsy.[6,7] The composition of the MA diet is similar to the classic ketogenic diet, with about a 1:1 ratio of fats to carbohydrates and protein. Because protein, fluids, and calories are not restricted, the MA diet is somewhat easier to administer and more "typical" foods are permitted.

The low glycemic index therapy (LGIT) diet allows 40 to 60 g/d of carbohydrates, or about 10% of daily calories, but includes only those carbohydrates that do not produce large fluctuations in blood glucose levels (glycemic index, <50). Protein and fats are more liberally available to patients with this diet compared with the ketogenic diet or the MA diet, making it more acceptable to many patients.

Indications and Contraindications for Dietary Therapies

Although a few reports introduce the ketogenic diet as a first-line therapy for infantile spasms,[8] most clinicians reserve this therapy for patients in whom several anticonvulsant medications fail to control the seizures.[9,10] The ketogenic diet might be particularly helpful for certain epilepsy syndromes, for example Dravet syndrome,[11] myoclonic atonic epilepsy,[10] and infantile spasms.[12] The ketogenic diet can be efficacious for focal and generalized epilepsies,[13] but children with focal epilepsies whose seizures do not respond to conventional treatment should undergo evaluation for epilepsy surgery if at all possible, because surgery could be curative.[14]

Although the ketogenic diet is considered one among a number of options for most patients, those with glucose transporter type 1 deficiency syndrome who are unable to use glucose adequately for cerebral metabolism require the ketogenic diet.[15] For these patients, the goal of therapy lies beyond simple seizure reduction, and higher than typical β-hydroxybutyrate levels are sought to optimize brain development. Patients with pyruvate dehydrogenase deficiency also benefit from treatment with the ketogenic diet because the diet allows bypass of the carbohydrate oxidation defect and can result in improved outcomes.[16] Disorders of fatty acid oxidation and carnitine metabolism and porphyria are absolute contraindications for a ketogenic diet and must be ruled out before diet initiation.[17]

Efficacy of the Dietary Therapies

When tolerated, a ketogenic diet can be more efficacious for some children with treatment-resistant epilepsy syndromes than additional medications. Neal et al[13] demonstrated significantly better seizure outcomes after 3 months of the ketogenic diet compared with standard medical therapies (38% of patients eating the ketogenic diet vs 6% of control subjects had >50% seizure reduction, with no difference between focal and generalized epilepsy syndromes). In a randomized controlled trial of 45 children receiving the classic diet and 49 receiving the MCT diet, nearly 10% had greater than 90% seizure reduction and about 20% enjoyed greater than 50% seizure reduction at 12 months, with no difference between the MCT and classic ketogenic diets.[18] Another randomized controlled trial showed no difference in seizure outcomes or biochemical profiles after 3 months among children assigned to a 4:1 (classic) or a 2.5:1 (modified) ketogenic diet.[19]

A Danish study of 33 consecutive patients treated with the MA diet found that more than half had greater than 50% seizure reduction during the first 3 months, comparable to the response rate among their patients receiving the classic ketogenic diet.[20] Children tolerated the MA diet well, without medically significant adverse effects, but families required intensive support from nurses, physicians, and dieticians to maintain their children on the diet. Kossoff et al[21] demonstrated better efficacy at 3 months among children whose MA diet included 10 g of carbohydrates per day compared with 20 g, but found improved tolerability in the latter group. The same authors showed that some children for whom the MA diet provides suboptimal control may experience improvement in their seizures with a transition from the MA to the classic ketogenic diet.[22]

Fewer studies of the LGIT diet are available, but these also demonstrate significant rates of improvement in seizure control. More than half of 76 patients experienced greater than 50% seizure reduction during 12 months of treatment.[23] To our knowledge, comparison trials of the LGIT and other dietary therapies have not been published (as of April 2012).

Although the primary clinical focus is typically on seizure outcomes, dietary treatments may exert additional beneficial effects. Parents reported improvement in quality of life and particularly in levels of alertness in a study of Danish children receiving the MA and ketogenic diets.[20] Early in their course, children receiving ketogenic diets can experience improvement in their interictal electroencephalogram (EEG) patterns, including resolution of hypsarrhythmia.[24] Animal models have suggested that the ketogenic diet has neuroprotective effects.[25]

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archpedi.jamanetwork.com/ on 05/06/2015

Adverse Effects of Dietary Therapies

Although many patients and families initially embrace dietary therapies as "natural" treatments for epilepsy, these diets are far from natural, and surveillance is required to minimize adverse effects. Most children will experience some adverse effects of dietary therapies, although the MA and LGIT diets might be better tolerated than the classic ketogenic diet. Virtually all children experience gastrointestinal tract adverse effects, especially constipation, but also nausea and vomiting. Hypercholesterolemia is common but can often be addressed by modifying fat sources (eg, decreasing butter in favor of coconut oil). Many families report initial fatigue or lethargy, but these effects usually resolve spontaneously. In their cohort of 50 patients receiving a ketogenic diet and 33 receiving an MA diet, Miranda et al[20] reported that about 75% experienced no significant adverse effects beyond the first week of treatment.

Diet Initiation and Surveillance

An excellent guideline outlines the ideal evaluation, initiation, and ongoing treatment for patients receiving the ketogenic diet and its variations.[17] Before patients start dietary therapies, families require extensive training, and baseline laboratory studies must be completed (and results found to be normal). Most centers initiate the classic ketogenic diet with an inpatient hospital admission. The admission allows for medical surveillance of hypoglycemia, dehydration, and acidosis, for example, and permits intensive education programs for caregivers. Traditionally, the ketogenic diet was initiated with a period of fasting. However, a randomized trial demonstrated that gradual initiation of the diet, by increasing the ratio of fats to carbohydrates and protein for several days, is equally effective and better tolerated.[26] One advantage of the LGIT and MA diets is that patients generally do not require hospital admission for diet initiation.

Intensive follow-up, including the combined efforts of the dietician and neurologist, are required to maintain dietary therapies. Patients must undergo assessment in person at regular intervals to measure growth variables and to evaluate adverse effects and efficacy. In addition, caregivers require frequent informal support via telephone calls and emails from nursing, dietary, and often social work staff. Follow-up care and laboratory testing should be tailored to meet individual patients' needs, but typically children must be examined in the clinic about every 3 months for the first year and then somewhat less frequently thereafter.[17]

Micronutrient status must be assessed regularly because the ketogenic and MCT diets are known to result in nutritional deficiencies,[27] some of which can result in clinically important symptoms. For example, Bergqvist et al[28] described a patient whose selenium deficiency, induced by ketogenic diet therapy, resulted in heart failure. Poor bone mineralization and levels of vitamin D below the laboratory reference range are known to be prevalent among patients with epilepsy, and these issues are exacerbated among those treated with ketogenic diets.[29]

SURGERY FOR TREATMENT-RESISTANT FOCAL EPILEPSY

Indications

Resective surgery may be indicated for children with treatment-resistant focal epilepsy if debilitating seizures continue despite appropriate antiseizure medications, and the potential benefit of seizure control outweighs the risk of resecting the cortex where the seizures originate (the epileptogenic zone). A careful presurgical evaluation is required to identify the epileptogenic zone and to determine whether resection of this area is likely to result in unacceptable new neurologic deficits. Removal of the epileptogenic zone is necessary and sufficient to achieve seizure freedom[30-32] and offers the best hope for a cure among appropriately selected patients. The ideal surgical candidate will have a single, well-localized focus of seizure onset in noneloquent cortex.

Presurgical Evaluation

The components of the presurgical evaluation are outlined in the **Table**. These data are evaluated by a multidisciplinary team, including neurologists, neurosurgeons, radiologists, psychologists, and social workers, to determine the best surgical strategy and the most likely risks and benefits of the proposed procedure.

Interictal and Ictal EEG. Interictal epileptiform discharge patterns can assist the clinician to refine the choice of further presurgical studies and are associated with a good surgical prognosis when unifocal.[33] Scalp EEG recorded during seizures often delineates the epileptogenic zone. In a study of 486 seizures among 72 children and adults in whom the epileptogenic zone location was verified by postoperative seizure freedom, ictal scalp EEG localized correctly in 72% of cases, more often in temporal than extratemporal epilepsy.[34] Emerging evidence, however, demonstrates that in the setting of a clear structural lesion, nonlocalizing and even nonlateralizing interictal or ictal EEG features do not preclude successful resective epilepsy surgery, which can treat children with severe epileptic encephalopathies.[35]

Neuroimaging. A combination of neuroimaging modalities is often used to complement and corroborate the EEG findings and increase the clinicians' confidence in the epileptogenic zone localization. The most widely used and reliable tool for identifying the ictal focus is magnetic resonance imaging (MRI). The presence of a distinct lesion on MRI can help to guide the pathway for surgical candidacy and predict a favorable surgical outcome.[36] High-resolution MRI may reveal brain lesions not detected on standard MRI scans. In general, T1-weighted, T2-weighted, gadolinium contrast, fluid-attenuated inversion recovery, coronal, and axial images should be obtained.[37] Quantitative MRI is reserved to measure hippocampal volume in mesial temporal sclerosis and is superior to qualitative MRI in mesial temporal sclerosis lateralization.[38]

When no lesion is identified on MRI, other noninvasive imaging modalities may delineate the epileptogenic

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archpedi.jamanetwork.com/ on 05/06/2015

Table. Presurgical Evaluation for Epilepsy Surgery Candidacy and Suggested Postsurgical Follow-up

Presurgical Evaluation	Postsurgical Follow-up[a]
History and physical examination	Follow up with neurosurgeon
Detailed seizure semiology	About 2 wk after surgery
Focal neurologic deficits	Outpatient epilepsy clinic visit
Epilepsy cause, if known	1-2 mo after surgery
	Weaning antiseizure medication therapy
	Considered on an individual basis, after 6-24 mo of postoperative freedom from seizures
Noninvasive EEG and video EEG	Routine-length EEG
Interictal scalp EEG	1-2 mo after surgery (coordinated with clinic visit)
Ictal scalp EEG	
Source localization: MEG[b]	
Neuroimaging	Considered on an individual basis
Structural imaging	
MRI	
Functional neuroimaging[b]	
PET	
SPECT	
Cognitive testing	Follow-up neuropsychometric testing
Speech and language assessment	Considered on an individual basis, particularly if cognitive difficulties are accentuated or persist after surgery
Neuropsychometric testing	
fMRI or Wada test[b]	
Social work evaluation	Social work evaluation
Insurance assessment	Reassess family functioning, educational environment, and need for additional resources
Optimize school placement and academic support	
Family support	

Abbreviations: EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

[a] Postoperative follow-up plans vary among institutions. This is a suggested schedule that should be tailored to individual patients.

[b] The decision to use source localization, functional neuroimaging, and fMRI testing is made on an individual basis and varies among institutions.

zone. A nuclear medicine technique, peri-ictal single-photon emission computed tomography (SPECT), and a subtraction image coregistered to MRI (SISCOM) may demonstrate a focal increase in blood flow at the time of a seizure, thereby localizing the region of seizure onset.[39,40] Guided by EEG monitoring, the SPECT tracer is injected immediately at the onset of a typical seizure, after which the ictal scan is obtained. The time to injection is critical, with decreasing data reliability as the time between seizure onset and tracer injection increases. Subsequently, the interictal SPECT scan is compared with the ictal image using SISCOM. In a study of children with polymicrogyria, SISCOM not only identified the location of the epileptogenic zone but also served as a primary prognostication tool for epilepsy surgery.[41]

Fludeoxyglucose F 18–labeled positron emission tomography and subsequent voxel-based analysis using statistical parametric mapping may localize areas of decreased cerebral metabolism, which are presumed to represent the epileptogenic zone.[42] For seizures caused by neuronal migration disorders and subtle cortical dysplasias, positron emission tomography and SPECT can be more sensitive than MRI.[43,44]

Magnetoencephalography is a relatively new functional imaging modality that delineates the epileptogenic zone by detecting magnetic fields produced by interictal epileptiform activity. Among 113 children and adults, magnetoencephalography accurately localized the epileptogenic zone in 58.8% of those with nonlocalizing EEG and 72.8% with partially localizing EEG.[45] In a recent study comparing presurgical diagnostic tests among children with nonlesional treatment-resistant focal epilepsy, magnetoencephalography and SISCOM were found to be better for localization than fludeoxyglucose F 18–labeled positron emission tomography.[46]

Cognitive Testing. All potential candidates for epilepsy surgery must undergo a neuropsychological assessment to evaluate presurgical cognition, the relationship of eloquent cortex to the epileptogenic lesion, and potential postsurgical deficits. Typically, a battery of standardized neuropsychometric tests is administered to evaluate general intelligence, attention, executive functioning, memory, behavior, and motor and sensory functions with a focused speech and language assessment.

For language and memory lateralization, additional testing is often required. The intracarotid amobarbital procedure (also known as Wada testing) involves injection of amobarbital sodium via invasive angiography into 1 carotid artery to inactivate the ipsilateral cerebral hemisphere temporarily, allowing memory and language testing of the contralateral hemisphere.[47] Functional MRI evaluates cerebral blood flow using the paramagnetic properties of deoxyhemoglobin, which decreases as blood flow increases (a technique called blood oxygenation level-dependent contrast). Functional MRI was recently shown to map language successfully with a 90% concordance with Wada test results and has replaced the Wada test in some epilepsy programs because fewer procedural risks are associated with functional MRI.[48,49]

Intracranial EEG. Intracranial EEG monitoring is most often used to refine the localization of extratemporal epileptogenic zones. Surgically placed subdural electrodes are used regularly for intracranial monitoring in infants and children. Such EEG monitoring can allow precise lo-

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archpedi.jamanetwork.com/ on 05/06/2015

calization of the seizure focus and an opportunity for cortical function mapping, minimizing the size of the resection and avoiding resection of eloquent cortex.

Resective Surgery and Related Procedures

Efficacy of Lesionectomy and Tailored Focal Resections. The efficacy and outcome of pediatric surgery varies widely depending on the procedure. However, seizure freedom is more likely among children with a lesion on imaging (81%) or histopathologic (73%) findings compared with children with nonlesional epilepsy (45%-46%), as demonstrated in a recent meta-analysis.[50]

Temporal lobectomy for mesial temporal sclerosis remains the most commonly performed epilepsy surgery because resection of the abnormal tissue is more effective in controlling seizures than standard medical management (58% vs 8% freedom from seizures among adults 1 year after the procedure in the single published randomized clinical trial).[51] No comparable efficacy trials have been performed among children, however, and most children who undergo resective surgery have extratemporal epilepsy or temporal lesions other than mesial temporal sclerosis.

Because the epileptogenic zone can extend beyond a visible brain lesion, a traditional lesionectomy may not be sufficient to render the patient free of seizures. Although a lesionectomy minimizes the resection of normal surrounding tissue, a tailored resection aims at maximizing the resection of electrically abnormal tissue and may extend beyond the borders of the visible lesion. No conclusive randomized studies compare lesionectomy with tailored resection, and the choice of procedure is individualized on a case-by-case basis, often guided by EEG data recorded from subdural electrodes.[52]

Brain Tumors. Patients with brain tumors can present with acute symptomatic seizures or chronic epilepsy. The most common epileptogenic neoplasms are low-grade tumors, including astrocytoma, mixed glioma, oligodendroglioma, and dysembryoplastic neuroepithelial tumor. Identification of these tumors has therapeutic and prognostic implications, with surgical resection offering the best survival outcome, reducing seizure burden, and limiting long-term effects of chemotherapy and radiation therapy.[53,54]

Hemispherectomy. Hemispheric malformations of cortical development primarily or exclusively involve a significant or a complete portion of 1 cerebral hemisphere and are characterized by treatment-resistant epilepsy, intellectual disability, and often contralateral hemiparesis. These malformations include hemimegalencephaly, porencephaly, and other similar but less well-characterized hemispheric malformations. Such lesions are often amenable to aggressive, early surgical intervention, with preservation of the child's cognitive functioning when seizures are controlled.

Rasmussen encephalitis is an acquired, slowly progressive disorder characterized by treatment-resistant focal seizures that may evolve into epilepsia partialis continua, worsening contralateral hemiparesis, and cognitive dysfunction, with corresponding progressive hemispheric atrophy.[55] However, for many patients, if initial focal resection or biopsy findings confirm the diagnosis, early hemispherectomy offers the best chance of transfer of function to the contralateral hemisphere and lowers the likelihood of secondary epileptogenesis.[56]

In general, rates of seizure freedom after hemispherectomy are lower among children with hemispheric malformations of cortical development than those with acquired disorders, such as Rasmussen encephalitis or ischemic stroke, because of commonly coexisting pathology.[57,58] Although seizure control is often improved, affected children will generally retain some degree of hemiparesis and other neurologic deficits, and long-term psychosocial functioning varies. In a recent prospective study of 53 children, hemispherectomy resulted in 65% seizure freedom after 5.4 years of follow-up, with minimal changes in cognitive variables.[59] Compared with the natural history of relentless progression for these severe epilepsy syndromes, aggressive surgical approaches can provide reasonably good outcomes.

Follow-up After Epilepsy Surgery

Postsurgical care varies widely among institutions. A suggested approach for short-term follow-up of children undergoing epilepsy surgery is outlined in the Table. Depending on the magnitude of the resection, patients may require short- or medium-term physical medicine and rehabilitation services. For those whose seizure outcome is favorable, medication therapy can often be slowly tapered after an appropriate waiting period (6-24 months, depending on the clinical scenario). Patients with persistent seizures may benefit from follow-up neuroimaging to evaluate for subtotal resection of the epileptogenic lesion. Additional surgery is sometimes an option if results of repeated EEG and imaging studies suggest that an improved outcome will be achieved. Dietary and/or neurostimulation treatments can also be considered.

PALLIATIVE EPILEPSY SURGERY PROCEDURES

For some children with challenging epilepsy syndromes, focal resection is not an option and complete seizure freedom is not the goal. Rather, reducing the seizure-related morbidity and thereby improving quality of life is a reasonable objective. Options can include corpus callosotomy or multiple subpial transections (MSTs).

Corpus Callosotomy

Corpus callosotomy is far from a new surgical technique, but it retains a role in palliation for some children with debilitating generalized seizures, particularly those with Lennox-Gastaut syndrome and frequent atonic seizures. After corpus callosotomy, freedom from seizures or more than 90% reduction was achieved in as many as 12 of 21 patients (57%) with atonic seizures (drop attacks).[60] For those patients who do not become seizure free, the remaining seizures are typically less disabling and result in fewer severe falls and injuries.

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archpedi.jamanetwork.com/ on 05/06/2015

Multiple Subpial Transection

Some patients cannot undergo epilepsy surgery because resection of primary speech, motor, sensory, or visual cortex would result in unacceptable functional deficits. To overcome this challenge, MST was developed. The MSTs interrupt the horizontal synchronizing neuronal networks while preserving vertical functional units. In 1 study, 12 of 26 children with varying neuropathologic findings (dysplasia, tumor, etc) who underwent limited cortical resection followed by MST became seizure free.[61] Although MST is being used with increasing frequency worldwide, its efficacy remains controversial, and this approach has not yet gained universal acceptance.[62]

NEUROSTIMULATION FOR TREATMENT-RESISTANT EPILEPSY

Despite the decades-long interest in neurostimulation for reducing seizure frequency and severity, the development of devices and procedures for clinical use is relatively recent. The most widely used and best known neurostimulation device is the vagus nerve stimulator (VNS). The VNS generator is implanted under the skin in the left pectoral area, with a wire leading to the left vagus nerve. The generator is programmed to deliver a current at regular intervals, with an option for manual activation to provide a stronger signal when needed, to abort seizures.

In the 1950s, animal studies showed that VNS reduced interictal epileptiform discharges.[63] The exact mechanism of antiseizure action is not well understood. Studies using SPECT have suggested that the VNS may mediate at least some of its effects via the thalamus.[64] Evoked responses in the thalamus triggered by VNS could influence thalamocortical pathways, thereby reducing seizure burden.[65]

Indications for VNS

In 1997, VNS was approved by the US Food and Drug Administration for adjunctive treatment of focal-onset seizures in patients older than 12 years. Studies have indicated VNS to be a well-tolerated and safe therapeutic option when resective epilepsy surgery is not feasible. Ideal candidates are those whose cognitive and motor abilities allow them to activate the device manually at the onset of a seizure. Children with persistent seizures who did not tolerate or are not candidates for dietary therapies or surgical options are also potential candidates.

Efficacy of VNS for Pediatric Epilepsy

Rossignol and colleagues[66] reported greater than 50% reduction in seizures in 19 of 28 children (68%) with treatment-resistant epilepsy treated with VNS. In another Canadian study, 15 of 41 subjects (37%) showed a 90% reduction in seizures with VNS therapy.[67] In addition to seizure reduction, VNS therapy was reported to result in improvement in seizure severity, faster recovery from seizures, and an overall improvement in quality of life in 12 of 15 subjects (80%).[68] These authors observed improvement in seizures in children with focal and generalized epilepsy syndromes.

Adverse Effects and Surveillance for Children Treated With VNS

Adverse effects of VNS include hoarseness of voice, coughing, or throat discomfort, all of which are usually transient. Gastroesophageal reflux is also commonly aggravated. Vagal nerve stimulation may exacerbate obstructive sleep apnea, and untreated apnea has adverse medical effects and can worsen seizure control. Thus, clinicians should screen for any history suggestive of sleep apnea when patients undergo evaluation for treatment with VNS.[69]

Other Neurostimulation Techniques

Other areas of the brain have also been targets of electrical stimulation for epilepsy treatment. Bilateral stimulation of the anterior thalamic nuclei reduced seizures in 56% of 54 adult subjects after 2 years of stimulation.[70] Direct stimulation of the cortical surface has also been attempted, particularly among individuals with focal epilepsy who are not surgical candidates. The basis of developing these techniques is interruption of epileptiform activity in the epileptogenic zone or the pathways along which seizures propagate.[71] In responsive neurostimulation, an implanted device analyzes the patient's EEG and delivers an electrical impulse when a specific EEG pattern (programmed by the clinician) is detected.[72] A study of 97 adults reported that responders showed a 38% reduction in seizures compared with a 17% reduction in controls.[73] Other therapies, such as low-frequency repetitive transcranial magnetic stimulation, have been shown to reduce seizure frequency, particularly in patients with cortical dysplasia,[74] and are promising developments for the future. Besides neurostimulation, other novel methods are being developed to treat seizures, such as localized cerebral hypothermia, local drug perfusion, and the use of optical (light) stimulation to cerebral cortex.[75] We are not aware of published data or any ongoing trials for any of these devices or methods in children (as of April 2012), but there is great interest in developing these technologies.

CONCLUSIONS

Despite the recent introduction of several new antiseizure medications, many children with epilepsy have treatment-resistant seizures. Evaluation by a pediatric epileptologist should be considered for these children to determine whether they may be candidates for dietary therapies, epilepsy surgery, or VNS. Although some of the epilepsy treatments discussed herein are not strictly "new," our understanding of their scientific underpinnings and the most appropriate and effective clinical applications of these treatments are rapidly expanding. Early and aggressive consideration of nonmedication therapies for treatment-resistant childhood epilepsy can identify some children whose seizures can be cured or significantly reduced, providing the best chance for optimal neurodevelopmental outcome and quality of life.

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archpedi.jamanetwork.com/ on 05/06/2015

Submitted for Publication: February 13, 2012; final revision received April 17, 2012; accepted April 18, 2012.
Published Online: November 12, 2012. doi:10.1001/jamapediatrics.2013.424
Correspondence: Sucheta M. Joshi, MD, MS, Department of Pediatric Neurology, Room 12-733, C. S. Mott Children's Hospital, 1540 E Hospital Dr, SPC 4279, Ann Arbor, MI 48109-4279 (suchetaj@med.umich.edu).
Author Contributions: *Study concept and design:* Joshi, Singh, and Shellhaas. *Analysis and interpretation of data:* Joshi, Singh, and Shellhaas. *Drafting of the manuscript:* Joshi, Singh, and Shellhaas. *Critical revision of the manuscript for important intellectual content:* Joshi, Singh, and Shellhaas. *Administrative, technical, and material support:* Joshi, Singh, and Shellhaas. *Study supervision:* Joshi, Singh, and Shellhaas.
Conflict of Interest Disclosures: None reported.

REFERENCES

1. Russ SA, Larson K, Halfon N. A national profile of childhood epilepsy and seizure disorder. *Pediatrics*. 2012;129(2):256-264.
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000;342(5):314-319.
3. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010;51(6):1069-1077.
4. Wheless JW. History of the ketogenic diet. *Epilepsia*. 2008;49(S8)(suppl 8):3-5.
5. Wilder RM. The effect of ketonemia on the course of epilepsy. *Mayo Clin Bull*. 1921;2:307.
6. Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. *Epilepsia*. 2006;47(2):421-424.
7. Smith M, Politzer N, MacGarvie D, McAndrews MP, Del Campo M. Efficacy and tolerability of the Modified Atkins Diet in adults with pharmacoresistent epilepsy: a prospective observational study. *Epilepsia*. 2011;52(4):775-790.
8. Kossoff EH, Hedderick EF, Turner Z, Freeman JM. A case-control evaluation of the ketogenic diet versus ACTH for new-onset infantile spasms. *Epilepsia*. 2008;49(9):1504-1509.
9. Patel A, Pyzik PL, Turner Z, Rubenstein JE, Kossoff EH. Long-term outcomes of children treated with the ketogenic diet in the past. *Epilepsia*. 2010;51(7):1277-1282.
10. Kilaru S, Bergqvist AGC. Current treatment of myoclonic astatic epilepsy: clinical experience at the Children's Hospital of Philadelphia. *Epilepsia*. 2007;48(9):1703-1707.
11. Caraballo RH, Cersósimo RO, Sakr D, Cresta A, Escobal N, Fejerman N. Ketogenic diet in patients with Dravet syndrome. *Epilepsia*. 2005;46(9):1539-1544.
12. Numis AL, Yellen MB, Chu-Shore CJ, Pfeifer HH, Thiele EA. The relationship of ketosis and growth to the efficacy of the ketogenic diet in infantile spasms. *Epilepsy Res*. 2011;96(1-2):172-175.
13. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomized controlled trial. *Lancet Neurol*. 2008;7(6):500-506.
14. Stainman RS, Turner Z, Rubenstein JE, Kossoff EH. Decreased relative efficacy of the ketogenic diet for children with surgically approachable epilepsy. *Seizure*. 2007;16(7):615-619.
15. Klepper J, Leiendecker B. GLUT1 deficiency syndrome: 2007 update. *Dev Med Child Neurol*. 2007;49(9):707-716.
16. Wexler ID, Hemalatha SG, McConnell J, et al. Outcome of pyruvate dehydrogenase deficiency treated with ketogenic diets: studies in patients with identical mutations. *Neurology*. 1997;49(6):1655-1661.
17. Kossoff EH, Zupec-Kania BA, Amark PE, et al; Charlie Foundation, Practice Committee of the Child Neurology Society; Practice Committee of the Child Neurology Society; International Ketogenic Diet Study Group. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. *Epilepsia*. 2009;50(2):304-317.
18. Neal EG, Chaffe H, Schwartz RH, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia*. 2009;50(5):1109-1117.
19. Raju KNV, Gulati S, Kabra M, et al. Efficacy of 4:1 (classic) versus 2.5:1 ketogenic ratio diets in refractory epilepsy in young children: a randomized open labeled study. *Epilepsy Res*. 2011;96(1-2):96-100.
20. Miranda MJ, Mortensen M, Povlsen JH, Nielsen H, Beniczky S. Danish study of a modified Atkins diet for medically intractable epilepsy in children: can we achieve the same results as with the classical ketogenic diet? *Seizure*. 2011;20(2):151-155.
21. Kossoff EH, Turner Z, Bluml RM, Pyzik PL, Vining EPG. A randomized, crossover comparison of daily carbohydrate limits using the modified Atkins diet. *Epilepsy Behav*. 2007;10(3):432-436.
22. Kossoff EH, Bosarge JL, Miranda MJ, Wiemer-Kruel A, Kang HC, Kim HD. Will seizure control improve by switching from the modified Atkins diet to the traditional ketogenic diet? *Epilepsia*. 2010;51(12):2496-2499.
23. Muzykewicz DA, Lyczkowski DA, Memon N, Conant KD, Pfeifer HH, Thiele EA. Efficacy, safety, and tolerability of the low glycemic index treatment in pediatric epilepsy. *Epilepsia*. 2009;50(5):1118-1126.
24. Kessler SK, Gallagher PR, Shellhaas RA, Clancy RR, Bergqvist AGC. Early EEG improvement after ketogenic diet initiation. *Epilepsy Res*. 2011;94(1-2):94-101.
25. Maalouf M, Rho JM, Mattson MP. The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. *Brain Res Rev*. 2009;59(2):293-315.
26. Bergqvist AGC, Schall JI, Gallagher PR, Cnaan A, Stallings VA. Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy. *Epilepsia*. 2005;46(11):1810-1819.
27. Christodoulides SS, Neal EG, Fitzsimmons G, et al. The effect of the classical and medium chain triglyceride ketogenic diet on vitamin and mineral levels. *J Hum Nutr Diet*. 2011;25(1):16-26.
28. Bergqvist AGC, Chee CM, Lutchka L, Rychik J, Stallings VA. Selenium deficiency associated with cardiomyopathy: a complication of the ketogenic diet. *Epilepsia*. 2003;44(4):618-620.
29. Bergqvist AGC, Schall JI, Stallings VA, Zemel BS. Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet. *Am J Clin Nutr*. 2008;88(6):1678-1684.
30. Cascino GD. Surgical treatment for extratemporal epilepsy. *Curr Treat Options Neurol*. 2004;6(3):257-262.
31. Wyllie E, Comair YG, Kotagal P, Bulacio J, Bingaman W, Ruggieri P. Seizure outcome after epilepsy surgery in children and adolescents. *Ann Neurol*. 1998;44(5):740-748.
32. Wyllie E, Chee M, Granström ML, et al. Temporal lobe epilepsy in early childhood. *Epilepsia*. 1993;34(5):859-868.
33. Holmes MD, Kutsy RL, Ojemann GA, Wilensky AJ, Ojemann LM. Interictal, unifocal spikes in refractory extratemporal epilepsy predict ictal origin and postsurgical outcome. *Clin Neurophysiol*. 2000;111(10):1802-1808.
34. Yoshinaga H, Ohtsuka Y, Abiru K, Nakano K, Oka E. Utility of scalp-recorded ictal electroencephalograms in childhood epilepsy with complex partial seizures. *Pediatr Int*. 2004;46(3):342-345.
35. Wyllie E, Lachhwani DK, Gupta A, et al. Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings. *Neurology*. 2007;69(4):389-397.
36. Mohamed A, Wyllie E, Ruggieri P, et al. Temporal lobe epilepsy due to hippocampal sclerosis in pediatric candidates for epilepsy surgery. *Neurology*. 2001;56(12):1643-1649.
37. Commission on Neuroimaging of the International League Against Epilepsy. Guidelines for neuroimaging evaluation of patients with uncontrolled epilepsy considered for surgery. *Epilepsia*. 1998;39(12):1375-1376.
38. Chuang NA, Otsubo H, Chuang SH. Magnetic resonance imaging in pediatric epilepsy. *Top Magn Reson Imaging*. 2002;13(1):39-60.
39. Lewis PJ, Siegel A, Siegel AM, et al. Does performing image registration and subtraction in ictal brain SPECT help localize neocortical seizures? *J Nucl Med*. 2000;41(10):1619-1626.
40. O'Brien TJ, So EL, Mullan BP, et al. Subtraction SPECT co-registered to MRI improves postictal SPECT localization of seizure foci. *Neurology*. 1999;52(1):137-146.
41. Wichert-Ana L, de Azevedo-Marques PM, Oliveira LF, et al. Ictal technetium-99 methyl cysteinate dimer single-photon emission tomographic findings in epileptic patients with polymicrogyria syndromes: a subtraction of ictal-interictal SPECT coregistered to MRI study. *Eur J Nucl Med Mol Imaging*. 2008;35(6):1159-1170.
42. Chugani DC, Chugani HT. New directions in PET neuroimaging for neocortical epilepsy. *Adv Neurol*. 2000;84:447-456.
43. Carne RP, O'Brien TJ, Kilpatrick CJ, et al. MRI-negative PET-positive temporal lobe epilepsy: a distinct surgically remediable syndrome. *Brain*. 2004;127(pt 10):2276-2285.
44. Hwang SI, Kim JH, Park SW, et al. Comparative analysis of MR imaging, positron emission tomography, and ictal single-photon emission CT in patients with neocortical epilepsy. *AJNR Am J Neuroradiol*. 2001;22(5):937-946.

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archpedi.jamanetwork.com/ on 05/06/2015

45. Pataraia E, Simos PG, Castillo EM, et al. Does magnetoencephalography add to scalp video-EEG as a diagnostic tool in epilepsy surgery? *Neurology*. 2004; 62(6):943-948.
46. Seo JH, Holland K, Rose D, et al. Multimodality imaging in the surgical treatment of children with nonlesional epilepsy. *Neurology*. 2011;76(1):41-48.
47. Powell GE, Polkey CE, Canavan AG. Lateralisation of memory functions in epileptic patients by use of the sodium amytal (Wada) technique. *J Neurol Neurosurg Psychiatry*. 1987;50(6):665-672.
48. Detre JA. fMRI: applications in epilepsy. *Epilepsia*. 2004;45(suppl 4):26-31.
49. Weber DA, Berl MM, Moore NN, et al. Temporal lobe epilepsy and cognition in children: will fMRI be of some help for a better understanding of the mechanisms involved? In: Arzimanoglou A, Aldenkamp A, Cross H, Lassonde M, Moshe´ N, Schmitz B, eds. *Cognitive Dysfunction in Children With Temporal Lobe Epilepsy*. Mont Rouge, France: John Libbey Eurotext; 2005:105-126.
50. Téllez-Zenteno JF, Hernández Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. *Epilepsy Res*. 2010;89(2-3):310-318.
51. Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med*. 2001;345(5):311-318.
52. Morris H III. Lesionectomy as a treatment for chronic epilepsy: is it sufficient for a good outcome? In: Luders H, Comair Y, eds. *Epilepsy Surgery*. 2nd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:967-971.
53. Babb TL, Brown WJ. Pathological findings in epilepsy. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies*. New York, NY: Raven Press; 1987:511-540.
54. Spencer DD, Spencer SS, Mattson RH, Williamson PD. Intracerebral masses in patients with intractable partial epilepsy. *Neurology*. 1984;34(4):432-436.
55. Bien CG, Granata T, Antozzi C, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain*. 2005;128 (pt 3):454-471.
56. Vining EP, Freeman JM, Brandt J, Carson BS, Uematsu S. Progressive unilateral encephalopathy of childhood (Rasmussen's syndrome): a reappraisal. *Epilepsia*. 1993;34(4):639-650.
57. Devlin AM, Cross JH, Harkness W, et al. Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. *Brain*. 2003;126(pt 3):556-566.
58. Kossoff EH, Vining EP, Pillas DJ, et al. Hemispherectomy for intractable unihemispheric epilepsy: etiology vs outcome. *Neurology*. 2003;61(7):887-890.
59. Pulsifer MB, Brandt J, Salorio CF, Vining EP, Carson BS, Freeman JM. The cognitive outcome of hemispherectomy in 71 children. *Epilepsia*. 2004;45(3):243-254.
60. Kim DS, Yang KH, Kim TG, et al. The surgical effect of callosotomy in the treatment of intractable seizure. *Yonsei Med J*. 2004;45(2):233-240.
61. Blount JP, Langburt W, Otsubo H, et al. Multiple subpial transections in the treatment of pediatric epilepsy. *J Neurosurg*. 2004;100(2 suppl; Pediatrics theme issue):118-124.
62. Obeid M, Wyllie E, Rahi AC, Mikati MA. Approach to pediatric epilepsy surgery: state of the art, I: general principles and presurgical workup. *Eur J Paediatr Neurol*. 2009;13(2):102-114.
63. Lulic D, Ahmadian A, Baaj AA, Benbadis SR, Vale FL. Vagus nerve stimulation. *Neurosurg Focus*. 2009;27(3):E5. doi:10.3171/2009.6.FOCUS09126.
64. Ring HA, White S, Costa DC, et al. A SPECT study of the effect of vagal nerve stimulation on thalamic activity in patients with epilepsy. *Seizure*. 2000;9(6):380-384.
65. Schachter SC. Vagus nerve stimulation: where are we? *Curr Opin Neurol*. 2002; 15(2):201-206.
66. Rossignol E, Lortie A, Thomas T, et al. Vagus nerve stimulation in pediatric epileptic syndromes. *Seizure*. 2009;18(1):34-37.
67. Benifla M, Rutka JT, Logan W, Donner EJ. Vagal nerve stimulation for refractory epilepsy in children: indications and experience at The Hospital for Sick Children. *Childs Nerv Syst*. 2006;22(8):1018-1026.
68. Hallböök T, Lundgren J, Stjernqvist K, Blennow G, Strömblad LG, Rosén I. Vagus nerve stimulation in 15 children with therapy resistant epilepsy; its impact on cognition, quality of life, behaviour and mood. *Seizure*. 2005;14(7):504-513.
69. Marzec M, Edwards J, Sagher O, Fromes G, Malow BA. Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients. *Epilepsia*. 2003; 44(7):930-935.
70. Fisher R, Salanova V, Witt T, et al; SANTE Study Group. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*. 2010;51(5):899-908.
71. Skarpaas TL, Morrell MJ. Intracranial stimulation therapy for epilepsy. *Neurotherapeutics*. 2009;6(2):238-243.
72. Sun FT, Morrell MJ, Wharen RE Jr. Responsive cortical stimulation for the treatment of epilepsy. *Neurotherapeutics*. 2008;5(1):68-74.
73. Morrell MJ, System RNS. in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology*. 2011; 77(13):1295-1304.
74. Hsu WY, Cheng CH, Lin MW, Shih YH, Liao KK, Lin YY. Antiepileptic effects of low frequency repetitive transcranial magnetic stimulation: a meta-analysis. *Epilepsy Res*. 2011;96(3):231-240.
75. Fisher RS. Direct brain stimulation is an effective therapy for epilepsy. *Neurology*. 2011;77(13):1220-1221.

©2013 American Medical Association. All rights reserved.

Downloaded From: http://archpedi.jamanetwork.com/ on 05/06/2015