Nonpharmacologic options for the treatment of epilepsy include epilepsy surgery, vagus nerve stimulation (VNS), and the ketogenic diet. Whereas the advantages and limitations of these treatment modalities have been extensively reviewed,1-3 there is no general consensus on when each option should be considered. For example, one of the most common questions asked by practicing neurologists is who should receive VNS and who should be evaluated for epilepsy surgery. What is the relative place of the nonpharmacologic treatments? How do they fit with respect to one another? We propose a hierarchic strategy of what to choose and when among nonpharmacologic treatments once medication treatment has been deemed a failure.

When to consider nonpharmacologic treatments. Currently, the first-line treatment of epilepsy remains antiepileptic drugs (AED). Exactly how many AED should be tried, in what combination, and for how long, before deeming epilepsy “intractable” is still debated, and there is no general consensus on how to define “medically intractable” epilepsy. It has been known for some time that the chances of control decline rapidly after the first few initial trials,4 and clinical practice supports the view that when the first few regimens fail, the chances of future control with AED drop precipitously. Several recent studies have documented this important concept. In a series of 74 patients with intractable localization-related epilepsy5 systematically tested with monotherapy using carbamazepine, phenytoin, phenobarbital, or primidone, only 9.5% achieved success (80% seizure reduction with improved quality of life). Another study6 reached a similar conclusion in children who had previously failed first-line agents as monotherapy and at least one combination, with only 10% of children benefiting from a drug regimen that had not been tried previously. Finally, it was recently confirmed that when the first AED is not effective, very few patients (11%) subsequently become seizure-free with further trials.7 Thus, there is now convincing evidence that intractability declares itself early, and that with each subsequent drug trial after the initial one, the chances of achieving control decline rapidly. Whereas the chances of success with new medications are probably never zero (i.e., a new drug may prove to be effective in a given patient), these data would support the idea that nonpharmacologic options should be examined early rather than as a last resort, as is generally recommended.1,7 It is also important to recognize that drug failure should be defined as either persistent seizures or seizure control obtained only at the expense of unacceptable side effects (i.e., being seizure free but unable to walk, think, or see because of side effects constitutes a drug failure). Finally, it should be emphasized that in addition to seizure severity and frequency, psychosocial morbidity may be important in the indication for nonpharmacologic treatments, including surgery.
For example, a seizure frequency of three per year is enough to prevent driving and can certainly affect employment. Thus, due to these multiple variables, drug failure should be ultimately decided on an individual basis and in conjunction with patients and their families. For the ensuing discussion, it is assumed that the neurologist and patient (or family) have agreed that medications have failed.

**First things first: An accurate diagnosis with EEG-video monitoring.** When AED fail and seizures continue, EEG-video monitoring should be performed. There is no strict cutoff for when EEG-video monitoring is indicated, but some guidelines have stated that referral to a specialized epilepsy center is appropriate if seizure control is not achieved within 9 months by the general neurologist.8 Certainly, if seizures are frequent (e.g., weekly or more), EEG-video monitoring would seem appropriate. In the vast majority of situations, the clinical data, EEG-video monitoring, and high quality MRI with dedicated epilepsy protocols allow the neurologist to achieve the following:

1. Confirmation of the diagnosis of epilepsy. This is critical, as a sizable 15 to 20% of patients referred for refractory seizures do not have epilepsy, but have psychogenic nonepileptic seizures.9

2. Determination of whether the epilepsy is localization-related or generalized, as defined by the International League Against Epilepsy.10

3. Distinguishing, among generalized epilepsies, between the idiopathic (formerly called primary, now better termed genetic11) type and the symptomatic (cause known) or cryptogenic (cause unknown), formerly called secondary, type.10,12,13

4. Differentiation, among localization-related epilepsies, between mesiotemporal and extratemporal/ neocortical epilepsy.

Based on this precise classification of the epilepsy syndrome (and not just the seizure type12), the options can then be examined and presented to the patient.

**Proposed algorithm.** See the figure for the proposed algorithm. There is some (limited) recent evidence that the ketogenic diet may be tolerated in adults, and that when tolerated it may be effective.14 However, it is unlikely that most adults can comply with this diet. Because localization-related epilepsy is the most common type encountered by adult neurologists, the main question when medications fail becomes how to choose between VNS and resective surgery.

1. **Localization-related epilepsy.** 1a. Mesiotemporal epilepsy (mesial temporal sclerosis [MTS]). This very common syndrome is associated with a 70 to 90% rate of success with resective surgery. The high degree of confidence with which success can be predicted preoperatively in MTS is illustrated by recent data. In a series15 of temporal lobectomies performed between 1962 and 1984, a striking 80% of patients had a class I or II outcome (65% seizure-free and...
15% class II) despite the fact that this was during the pre-MRI era. It is easily conceivable then that in the current days of imaging, using dedicated and sensitive MRI protocols, the success can be over 90% and predicted preoperatively, as has been well documented. However, in fact, with the large experience accumulated with the excellent outcome of surgery for MTS, it may even be considered, in some cases, to offer temporal lobectomies based only on interictal EEG and MRI, as has been proposed. In addition to the excellent seizure outcome, neurologic complications after temporal lobectomies are rare. Neurological deficits following temporal lobectomies are always a potential concern and have been extensively studied. Whereas language and memory deficits occur, particularly after dominant side resections, they are usually transitory and mild. Furthermore, neuropsychological deficits after temporal lobectomy are even less pronounced in MTS than other etiologies. Thus, it is generally accepted that possible minor deficits are usually a worthwhile trade-off given the preoperative seizure burden of these patients. It should be pointed out that “routine” MRI are frequently “normal” when performed at the time of the first seizure, as their purpose at that time is to exclude gross structural lesions (e.g., brain tumor, vascular malformation). However, when the neuroradiologist is informed in advance that the patient is a candidate for resective surgery, then additional imaging sequences may be performed, increasing the likelihood that an abnormality will be identified. Thus, normal MRI for the purpose of this algorithm refers to sophisticated MRI employing a dedicated epilepsy protocol, and preferably focusing on the area of suspected seizure onset based on EEG-video monitoring.

1b. Nonmesiotemporal epilepsy. This category includes extratemporal and temporal neocortical syndromes. In this situation, the critical determinant is structural imaging—i.e., MRI—which will divide cases into lesional and nonlesional. It should be the purpose of this algorithm refers to sophisticated MRI employing a dedicated epilepsy protocol, and preferably focusing on the area of suspected seizure onset based on EEG-video monitoring.

1b1. Lesional nonmesiotemporal epilepsy. When MRI uncovers a subtle lesion in an area consistent with the seizure semiology and EEG findings, then resective surgery has a significant success rate and should be pursued. Specifically, postoperative seizure outcome for these cases is almost as good as that of temporal lobectomies. This is true for various lesions, and excellent outcomes (seizure-free or almost seizure-free) have been reported in 70% of cases for vascular malformations, in 70% of cases for encephalomalacia, and in 63 to 79% of cases for neoplasms. Numbers are somewhat lower for cortical dysplasias, ranging from 35 to 42%. Success rates are also comparable among various lobar locations. In contrast to these chances of an excellent seizure outcome, results with VNS are less ambitious with a reduction in seizure frequency of 25 to 35%, a 50% reduction in 30 to 40% of patients, and a seizure free outcome in a negligible fraction of patients. Resective surgery in these cases may or may not require the use of invasive (intracranial) EEG, depending on the totality of the noninvasive evaluation (surface EEG-video, MRI, functional imaging). If invasive EEG is necessary, it is usually focused and dictated by the lesion and the seizure semiology, so that it may be relatively uncomplicated, and sometimes limited to functional mapping. In many cases, a lesionectomy will also result in significant improvement. Thus, overall, VNS is generally a less optimal option in this scenario, as has been acknowledged, and should probably be reserved for surgical failures. There are additional factors that may influence the strategy and make this scenario variable. For example, the suspected or uncertain pathologic diagnosis of the lesion (e.g., neoplasm) may in itself be an argument for surgical intervention (for “lesional” rather than seizure-related reasons), and the lesion size, location, and surgical accessibility may also influence the decision.

1b2. Nonlesional nonmesiotemporal epilepsy. In the presence of a normal MRI, nonmesiotemporal focal epilepsy has a guarded outcome with resective surgery, and when surgical treatment is pursued, it requires invasive EEG. Therefore, although workup for a possible resection may be considered, these cases could also be treated with VNS. This view is consistent with the guidelines and assessment issued by the American Academy of Neurology. Should VNS fail, resective surgery may be considered. How to choose at this stage between invasive EEG and VNS largely depends on the information obtained with the noninvasive evaluation.

1b2a. Strong lateralizing evidence. If there is strong lateralizing evidence that allows confident lateralization to a hemisphere, it may be reasonable to pursue invasive EEG for a possible resection. Evidence for lateralization may come from various lines of evidence. First, clinical data (seizure semiology) can provide confident lateralization, and many lateralizing signs have been described. To a lesser degree, the neurologic examination and a neuropsychological evaluation may provide some lateralizing information. Functional imaging studies such as PET or SPECT, sometimes combined with MRI, may also give strong lateralizing information. Finally, EEG in these cases is often lateralized without being further localized within a hemisphere. Surgical outcome in this group is not nearly as good as in temporal cases. Therefore, VNS would also be an appropriate alternative, with less risk but also less potential benefits. This scenario (i.e., clear nonmesiotemporal localization with definite lateralizing features) is relatively common at referral epilepsy centers, and is probably one where much variability exists in the approach among various epileptologists.
162b. Absence of strong lateralizing evidence. In the absence of any lateralizing feature, the search for a single resectable epileptogenic zone amounts to what is commonly referred to as a “fishing expedition,” and these cases probably should generally not be pursued for resection. Here VNS appears to be the treatment of choice.

2. Generalized epilepsy. 2a. Idiopathic generalized epilepsy. The idiopathic generalized epilepsies (IGE) were initially defined as having no identifiable cause and a “presumed genetic etiology” but it has now become clear and well accepted that they are genetic in origin. These epilepsies generally respond to medications, in over 80% of cases. However, the IGE are occasionally misdiagnosed as partial epilepsies and treated with the wrong AED (e.g., phenytoin, carbamazepine, gabapentin, tiagabine), to which they may not respond. The first-line AED for IGE is classically valproate. When valproate fails, either because of toxicity or lack of efficacy, other options are emerging using “broad-spectrum” AED such as lamotrigine and topiramate and possibly zonisamide or levetiracetam. In general, this type of epilepsy should not require treatments other than medications. There is limited evidence that VNS may be an effective option. However, because IGE are frequently benign and outgrown, VNS should be reserved for exceptionally refractory cases of IGE and in adults only. Brain surgery is never an option for the IGE.

2b. Symptomatic/cryptogenic generalized epilepsy. These epilepsies, the prototype of which is the Lennox–Gastaut syndrome, are notoriously difficult to treat. They are frequently intractable to multiple AED regimens. The only surgery that may be effective is a corpus callosotomy, which works primarily for tonic and tonic seizures. In this situation, three possibilities exist that are not mutually exclusive. Corpus callosotomy and the ketogenic diet have been used mostly in this setting. VNS has been shown effective and has the advantage that it can also improve quality of life (a subjective measure) without the cognitive and behavioral side effects of increased AED. This is particularly important, as patients with this type of epilepsy are typically mentally subnormal. Because this group of epilepsy is so often multifocal and intractable, and despite the fact that this was not the original indication for VNS, this may well be its best indication. Based largely on the degree of invasiveness and risks, the ketogenic diet and VNS appear to be a reasonable first line of treatment, whereas corpus callosotomy should be considered second line.

Limits of the algorithm. We recognize that not all patients with epilepsy require EEG-video monitoring. However, this algorithm deals with epilepsy that has not responded to treatment, and we believe that when medications fail, EEG-video monitoring should be performed. Although (for example) the Food and Drug Administration does not require ictal recordings for the use of VNS, we would not recommend any invasive procedures, including VNS, without verification of the diagnosis by EEG-video monitoring. This is also in agreement with the assessment issued by the American Academy of Neurology, which recommends VNS for patients who are not candidates for resective surgery, a determination that can only be made with EEG-video monitoring.

We recognize that when conventional therapies fail, patients with refractory chronic conditions may occasionally turn to alternative medicine, and epilepsy is no exception. At this point, there is no evidence that unconventional therapies are of value for intractable epilepsy, and this proposal was purposely limited to modalities that have been evaluated and accepted as standards of care.

The respective place of nonpharmacologic treatment for medically intractable epilepsy is still evolving. This algorithm is based on what is known of the various nonpharmacologic therapies in regards to efficacy and side effects. We recognize that many other factors may come into play that are not taken into account in this algorithm. These include economic arguments, the constraints of insurance companies and third party payers, and individual preferences of patients and families. We recognize that the choice of therapy is ultimately that of patients and their families. Choices must be presented to them. This proposed algorithm is meant to propose rational choices based on the known risk/benefit ratio for various treatment modalities.

References


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