# VAGUS NERVE STIMULATION FOR GENERALIZED EPILEPSY?. . .SHOW ME THE EVIDENCE!

**Is Vagus Nerve Stimulation a Treatment Option for Patients with Drug-Resistant Idiopathic Generalized Epilepsy?** Kostov H, Larsson PG, Røste GK. *Acta Neurol Scand Suppl* 2007;187:55–58. BACKGROUND: The value of vagus nerve stimulation (VNS) for treating patients with drug-resistant idiopathic generalized epilepsy (IGE) is not well documented. PATIENTS AND METHODS: Twelve patients (2 males, 10 females) with a mean age of 31 years (11–48 years) and with drug-resistant IGE had VNS implanted in the period 1995–2006. All had generalized seizures documented by video-electroencephalogram. Mean follow-up period was 23 months (9–54 months). RESULTS: There was a total seizure reduction of 61% ($p = 0.0002$). There was 62% reduction of generalized tonic–clonic seizures ($p = 0.0020$), 58% of absences ($p = 0.0003$), and 40% of myoclonic seizures ($p = 0.0156$). Eight patients were considered responders (>50% seizure reduction); two of these patients became seizure-free. Five out of seven patients with juvenile myoclonic epilepsy were responders. At the last follow-up visit, the patients had reduced the antiepileptic drug (AED) usage from an average of 2.3 to 1.7 AED per patient ($p = 0.0625$). Two patients are currently being treated with VNS therapy only. Nine patients reported side effects, which were mostly mild and tended to diminish over time. CONCLUSION: Our results indicate that adjunctive VNS therapy is a favorable treatment option for patients with drug-resistant IGE. Rapid cycling seems worth trying in some of the nonresponders.

## COMMENTARY

In 1999, the Therapeutics and Technology Assessment (TTA) subcommittee of the American Academy of Neurology published a guideline for the use of vagal nerve stimulation (VNS) in epilepsy. On the bases of two multicenter randomized studies, the TTA found VNS to be an acceptable therapy for adults and adolescents over 12 years of age with medically intractable partial seizures who are not candidates for potentially curative surgical resections, such as lesionectomies or mesial temporal lobectomies (1). The two studies compared the antiepileptic effect of high versus low intensity stimulation (frequency: 20–50 vs 1–2 Hz; pulse-width: 500 microseconds vs 130 microseconds; on time: 30–90 seconds vs 30 seconds; off time: 5–10 minutes vs 60–180 minutes; current: 0.25–3.0 mA vs 0.25–2.75mA) during a 3-month period, while maintaining a constant use of concomitant antiepileptic drugs (AEDs) (2,3). Relative to a 3-month baseline seizure frequency, patients randomized to high stimulation had a significantly greater reduction in seizures than patients randomized to the low stimulation group (24% vs 6% and 28% vs 15% in the first and second study, respectively). Since the publication of the TTA guidelines, there have been several open trials reporting on VNS for the treatment of Lennox–Gastaut syndrome and pharmacoresistant idiopathic generalized epilepsy (IGE)—one of which is the article by Kostov et al. reviewed here. Unfortunately, no new recommendations would come from updating the 1999 guidelines today, as the methodology used in all of these studies fails to meet the necessary criteria to establish a positive recommendation for the use of VNS for these types of epilepsy. Thus, should the published data on the use of VNS for generalized epilepsies be ignored?

The available data on the impact of VNS in Lennox–Gastaut syndrome consist of two retrospective studies and one prospective open trial in which seizure rate reductions ranged from 27 to 64 percent (4–6). The first retrospective study included 13 patients (mean age 16.7 years), for whom VNS yielded a median seizure rate reduction of 52% (range, 0–93%; $p = 0.04$) during the first 6 months of treatment (4). A second retrospective study of 50 children from six epilepsy centers (median age 13 years) found median reductions in total seizures of 58% at 6 months (5). In the only prospective study of 16 children during which AEDs were held constant, a reduction in seizure frequency of 50% or greater was identified in 25% of the patients (6). This study also compared measures of behavior, mood, and cognitive functions, and the data suggested a moderate improvement in all three areas. Furthermore, the scores for mood and mental age improved independent of seizure control. Of note, the latter study, which was methodologically sounder, yielded the least impressive seizure reduction results. These data have been sufficient to convince

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many epilepsy centers to consider VNS for the treatment of Lennox–Gastaut syndrome ahead of corpus callosotomy. In the case of pharmacoresistant IGE, two small open trials (one of which is the prospective trial by Kostov and colleagues) reported a seizure frequency reduction ranging from in 57 to 62 percent (7). Two other prospective studies reported on the use of VNS in open trials in a mixed group of 16 (8) and 24 (9) patients with refractory IGE or Lennox–Gastaut syndrome. There was a median overall seizure rate reduction of 46% and 43%, respectively.

The structures in the brain affected by VNS play important roles in the pathogenic mechanisms of partial and generalized epilepsies and, theoretically, effects on these structures ought to support use of VNS as a viable treatment. Such is the case for the thalamocortical networks. For example, in a study with $O_{15}$-$H_20$-PET, VNS was found to activate the thalamus in patients with refractory partial epilepsy; the highest seizure rate reductions occurred in patients who had the greatest increases in thalamic blood flow (10).

Similarly, neuroimaging studies on humans with IGE have documented structural and functional abnormalities in the thalamus. For example, proton magnetic resonance spectroscopic imaging, measuring N-acetylaspartate (NAA), choline-containing compounds, and creatine (Cr) was used in 20 patients with IGE and 20 age-matched healthy subjects. Measurements were made in the thalamus, insular cortex, the posterior temporal lobe white matter, and the splenium of the corpus callosum. A reduction in the mean NAA/Cr was found in the thalamus of IGE patients but not in other examined areas (11). In addition, there was a significant negative correlation between thalamic NAA/Cr and duration of epilepsy, but no differences were found between patients with persistent or controlled seizures. The investigators suggested that the results provided evidence of progressive thalamic neuronal dysfunction in patients with IGE, supporting the notion of abnormal thalamocortical circuitry as a substrate of seizure generation in this form of epilepsy.

Furthermore, VNS increases the secretion of norepinephrine in various structures of the brain. The pathogenic role of norepinephrine has been demonstrated in several animal models of generalized epilepsy, particularly in two strains of genetically epilepsy-prone rats (GEPR-3 and GEPR-9) (12). Of note, the GEPR-9 strain displays more severe seizures and has greater norepinephrine deficits in several brain areas (i.e., cerebellum, pons-medulla, thalamus, and possibly the temporal cortex and olfactory bulbs). Suppression of convulsions was obtained with intracerebroventricular injections of norepinephrine in both strains, while intraventricular norepinephrine tissue grafts were successful in reducing seizure severity of audiogenic seizures. By the same token, in experimental animal models of epilepsy, the anticonvulsant effect of VNS was associated with noradrenergic mechanisms (12). Indeed, chronic depletion of norepinephrine with bilateral infusion of 6-hydroxydopamine into the noradrenergic neurons of the locus coeruleus in the rat significantly prevented or reduced the anticonvulsant effect of VNS against electroshock or pentylenetetrazol-induced seizures.

Clearly, there are enough experimental and clinical data to suggest that VNS could be an effective therapy for generalized epilepsies. However, pivotal studies are missing and no definite recommendation can be made until they are carried out and shown to demonstrate a therapeutic effect. The medical and scientific communities are waiting for such recommendations.

*by Andres M. Kanner, MD*

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# CHANNELING INTO THE EPILEPSIES

**The Spectrum of SCN1A-Related Infantile Epileptic Encephalopathies**. Harkin LA, McMahon JM, Iona X, Dibbens L, Pelekanos JT, Zuberi SM, Sadleir LG, Andermann E, Gill D, Farrell K, Connolly M, Stanley T, Harbord M, Andermann F, Wang J, Batish SD, Jones JG, Seltzer WK, Gardner A; Infantile Epileptic Encephalopathy Referral Consortium, Sutherland G, Berkovic SF, Mulley JC, Scheffer IE. *Brain* 2007;130(Pt 3):843–852. The relationship between severe myoclonic epilepsy of infancy (SMEI or Dravet syndrome) and the related syndrome SMEI-borderlands (SMEB) with mutations in the sodium channel alpha 1 subunit gene *SCN1A* is well established. To explore the phenotypic variability associated with *SCN1A* mutations, 188 patients with a range of epileptic encephalopathies were examined for *SCN1A* sequence variations by denaturing high performance liquid chromatography and sequencing. All patients had seizure onset within the first 2 years of life. A higher proportion of mutations were identified in patients with SMEI (52/66; 79%) compared to patients with SMEB (25/36; 69%). By studying a broader spectrum of infantile epileptic encephalopathies, we identified mutations in other syndromes including cryptogenic generalized epilepsy (24%) and cryptogenic focal epilepsy (22%). Within the latter group, a distinctive subgroup designated as severe infantile multifocal epilepsy had *SCN1A* mutations in three of five cases. This phenotype is characterized by early onset multifocal seizures and later cognitive decline. Knowledge of an expanded spectrum of epileptic encephalopathies associated with *SCN1A* mutations allows earlier diagnostic confirmation for children with these devastating disorders.

## COMMENTARY

An increasing number of human neurological diseases have been identified that are due to brain ion channel dysfunction, the neurological channelopathies. Often after the first discovery that a particular phenotype is associated with a dysfunctional channel, further work leads to the recognition of a wider range of phenotypic variation. Appreciation of the full phenotypic spectrum can be very important clinically and can shed light on fundamental disease mechanisms. The present study reveals a wider phenotypic range of diseases linked to neuronal sodium channel dysfunction.

The epileptic encephalopathies are a group of devastating disorders that encompass both idiopathic conditions, such as West syndrome (infantile spasms), and genetic disorders, such as severe myoclonic epilepsy of infancy (SMEI). Patients undergo a relentless neurological decline and their seizures often are difficult to treat. SMEI (also known as Dravet syndrome) is a rare disorder characterized by generalized tonic, clonic, and tonic–clonic seizures, which are initially induced by fever and develop during the first year of life. Later, other seizure types develop, including absence, myoclonic, and simple or complex partial seizures, which culminate in a malignant epileptic syndrome. Psychomotor development becomes abnormal during the second year. Those patients who do not fulfill the entire diagnostic criteria for SMEI have been referred to as SMEI-borderland or SMEB.

Mutations in the sodium channel $\alpha_1$ subunit gene, *SCN1A*, were first identified in patients with generalized epilepsy with febrile seizures plus (GEFS+) syndrome, a relatively benign inherited epilepsy syndrome (1). *SCN1A* encodes the $\alpha_1$ subunit of the neuronal voltage-gated sodium channel $Na_v1.1$, which is responsible for propagation of action potentials. Since the initial report, mutations in the sodium channel $\alpha_1$ subunit have also been identified in patients with SMEI (2) and other epileptic encephalopathies, such as infantile spasms (3) and more recently postvaccine encephalopathy (4). These sporadic and autosomal dominant epilepsy syndromes are now thought to represent different ends of the phenotypic spectrum of *SCN1A* mutations. Confusingly, epilepsy-associated mutations can lead to both a loss and a gain of function of $Na_v1.1$ in vitro (5). Thus, the downstream result of opposite alterations in sodium currents presumably has different effects on inhibitory and excitatory neuronal networks, leading to the common final pathway of epileptogenesis.

Many *SCN1A* mutations have been identified in patients with SMEI, usually these occur de novo (6,7). In this comprehensive study, Harkin et al. have analyzed a cohort of 188 patients with various epileptic encephalopathies and have provided extensive clinical and EEG phenotypes (8). Patients were screened for mutations in *SCN1A*, mainly by direct DNA sequencing. Mutations were identified in 48% of patients. Of the 90 mutations, 72 were novel, all affecting conserved parts of the channel protein, and 96% occurred de novo. No patients with West syndrome, infantile spasms, myoclonic encephalopathies, progressive myoclonic epilepsy, alternating hemiplegia, or unclassified epilepsy syndromes had a *SCN1A* mutation. However, mutations were not restricted to those with typical epileptic encephalopathy. Interestingly, six patients (24%) with cryptogenic generalized epilepsy, three (8%) with cryptogenic focal epilepsy, two (20%) with myoclonic–astatic, and one (8%) with Lennox–Gastaut syndrome also carried mutations. Some of these patients had a normal intellect and/or no

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associated neurological deficit. The majority of mutations were found in patients with SMEI or SMEB. Pooling the cases in their study gives a detection rate of 75.4% for SMEI/SMEB, which is comparable to a recent report of 71% in SMEI/SMEB, of which 82% were de novo (9). The mutation types also were in keeping with the published literature, with SMEI more often associated with nonsense or splice site mutations (61%) and SMEB a result of missense mutations (52%). In both SMEI and SMEB, missense mutations clustered in the transmembrane segments of the protein, as has been shown previously.

This important paper widens the phenotypic spectrum of *SCN1A* mutations: GEFS+ and a recent report of a family with febrile seizures and TLE (10) represent the milder side; intractable childhood epilepsy with generalized tonic–clonic seizures (5) and some patients with cryptogenic epilepsies (8) now are included in the middle ground; while added to the severe end of the spectrum with the epileptic encephalopathies of SMEI/SMEB, are Lennox-Gastaut syndrome, myoclonic–astatic epilepsy, and postvaccine encephalopathy (4). Providing a definitive genetic diagnosis for these children can be helpful, both by directing appropriate treatment (for example, lamotrigine and carbamazepine may make seizures worse) but also by avoiding further unnecessary and invasive investigations. Although there are currently no gene-specific anticonvulsants, such treatments may be available in the future.

While many different *SCN1A* mutations have been identified in patients with SMEI, most of which are unique to individuals, several recurrent mutations have also been found (7). Mutations are spread throughout the gene and, therefore, have different predicted functional effects on the protein (11). However, it is apparent that wherever and whatever the functional effects of these mutations are, they all lead to a similar seizure phenotype. Collating the available functional data on such mutations does not lead to an obvious explanation of the shared epilepsy phenotype; however, mathematical modeling has predicted an increased excitability via augmented action potential firing (12). Mutations in *SCN1A* are the most numerous genetic cause of epilepsy; hence further efforts to clarify their precise pathophysiology are likely to be important to the fundamental understanding of epileptogenesis.

*by Tracey D. Graves, MD, and Michael G. Hanna, MD*

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# MULTIPLE AURAS: NOT AN OMINOUS SIGN FOR EPILEPSY SURGERY

**Multiple Auras: Clinical Significance and Pathophysiology.** Widdess-Walsh P, Kotagal P, Jeha L, Wu G, Burgess R. *Neurology* 2007;69(8):755–761. Erratum in: *Neurology* 2007;69(19):1890. BACKGROUND: Patients with partial epilepsy may report multiple types of aura during their seizures. The significance of the occurrence of multiple auras in the same patient is not known. METHODS: The clinical and electrophysiologic characteristics of patients with more than one aura type (abdominal, auditory, autonomic, gustatory, olfactory, psychic, somatosensory, and visual auras), evaluated in the Cleveland Clinic epilepsy monitoring unit between 1989 and 2005, were studied. RESULTS: Thirty-one patients experienced multiple aura types during a seizure. Ninety percent of patients with at least two aura types ($n = 31$) and 100% of patients with at least three aura types ($n = 12$) had seizures arising from the right/nondominant hemisphere. EEG seizures remained restricted in all patients during their auras. Twenty patients had epilepsy surgery with seizure freedom in 53%. Subdural EEG recordings in six patients showed either a march of sequential auras, or in one case, several ictal onset zones resulting in separate isolated auras. Ictal SPECT in six patients with right-sided seizures showed a lack of activation in brainstem structures. CONCLUSIONS: Most patients who report multiple aura types have localized epilepsy in the nondominant hemisphere, and are good surgical candidates. A common mechanism for multiple auras may be a spreading but restricted EEG seizure activating sequential symptomatogenic zones, but without the ictal activation of deeper structures or contralateral spread to cause loss of awareness and amnesia for the auras.

## COMMENTARY

The seizure aura reflects the initial involvement of nonsilent cortex after seizure onset. Although the initial symptoms may result activation of distant cortex following seizure propagation, they remain very useful for localization of the epileptogenic zone, in conjunction with other tests, during the presurgical evaluation. Some categories of auras have localizing and lateralizing value (1). For example, a visual aura with elementary visual hallucinations favors an occipital origin (2), a unilateral somatosensory aura suggests contralateral sensory cortex localization (3), an elementary auditory aura supports a lateral temporal lobe involvement (4,5), and olfactory (6) as well as abdominal (7) auras are most commonly associated with mesial temporal foci.

A report by the same patient of more than one aura raises concern for the presence of more than one seizure focus. Multiple auras can occur in different seizures or in the same seizure. Widdess-Walsh and colleagues specifically addressed multiple auras within the same seizure, either occurring simultaneously or sequentially. The authors found that a single epileptogenic zone was usually responsible for these phenomena and that the presence of multiple auras in the same seizure is not a negative prognostic indicator for epilepsy surgery. Some patients in the study received in-depth investigations with intracranial recordings or ictal single photon emission computed tomography, shedding light on the mechanism of multiple auras: multiple auras in the same seizure appear to be related to preservation of consciousness during seizure propagation. The multiple auras appear to be experiences from sequential or simultaneous activation of multiple symptomatogenic zones.

All patients in the Widdess-Walsh et al. study with multiple auras had temporal or posterior quadrant foci. Patients with multiple auras and temporal foci often had somatosensory or visual auras, which may be a concern for parietal or occipital origin. However, somatosensory or visual auras usually followed abdominal, psychic, olfactory, or gustatory auras, which are typically associated with temporal lobe origin. Other studies have suggested that somatosensory or visual auras may occur with temporal lobe epilepsy (8,9), but at least some of the patients in these studies also had other symptoms more typical of temporal lobe origin, indicating multiple auras. Thus, the localizing value of an aura is reduced if it is not the first seizure manifestation.

Patients are more likely to remember their aura if the seizure is restricted and less likely to remember it if the following seizure is widespread or severe (10). In the study by Widdess-Walsh et al., it is interesting that the vast majority of patients with multiple auras had right hemisphere foci and seizures that tended to remain restricted to one hemisphere. Right temporal lobe seizures are generally less likely to affect consciousness than left temporal lobe seizures. The preservation of ictal responsiveness in association with automatisms is suggestive of right temporal lobe epilepsy (11). Thus, it is not surprising that the longer preservation of awareness during propagation of right temporal lobe seizures could lead to more ictal symptoms.

The study of Widdess-Walsh and colleagues did not address the situation of multiple auras not occurring in the same seizure. Intuitively, if some seizures start with one aura type and others start with a different aura type, the presence of distinct seizure foci is suggested. This finding could be a negative indicator with respect to epilepsy surgery candidacy. However, it is possible that different single auras reflect different propagation pathways

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from the same focus. This phenomenon of distinct single auras also deserves formal study.

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# Suicide in Patients with Epilepsy

**Epilepsy and Risk of Suicide: A Population-Based Case–Control Study.** Christensen J, Vestergaard M, Mortensen PB, Sidenius P, Agerbo E. *Lancet Neurology* 2007;6(8):693–698. BACKGROUND: Studies have linked epilepsy with an increased suicide risk, but the association might be modified by psychiatric, demographic, and socioeconomic factors. METHODS: Suicide cases were identified in the Cause of Death Register in Denmark from 1981 to 1997. Up to 20 controls, matched by sex, birth year, and calendar date, were assigned to each suicide case. FINDINGS: We identified 21,169 cases of suicide and 423,128 controls. In total, 492 (2.32%) individuals who committed suicide had epilepsy compared with 3,140 (0.74%) controls, corresponding to a three times higher risk (rate ratio [RR] 3.17 [95% CI 2.88–3.50]; $p < 0.0001$). The RR remained high after excluding those with a history of psychiatric disease and adjusting for socioeconomic factors (1.99, 1.71–2.32; $p < 0.0001$). The highest risk of suicide was identified in patients with epilepsy and comorbid psychiatric disease, even after adjusting for socioeconomic factors (13.7, 11.8–16.0; $p < 0.0001$). In individuals with epilepsy, the highest risk of suicide was found during the first half year after diagnosis was made (5.35, 3.43–8.33; $p < 0.0001$), and was especially high in those with a history of comorbid psychiatric disease (29.2, 16.4–51.9; $p < 0.0001$). INTERPRETATION: Individuals with epilepsy have a higher risk of suicide, even if coexisting psychiatric disease, demographic differences, and socioeconomic factors are taken into account. Our study identifies people with newly diagnosed epilepsy as a vulnerable group that require special attention.

**Depression and Suicide in Epileptic Victims: A Population-Based Study of Suicide Victims during the Years 1988–2002 in Northern Finland.** Mainio A, Alamäki K, Karvonen K, Hakko H, Särkioja T, Räsänen P. *Epilepsy Behav* 2007;11:389–393. Patients with epilepsy are known to have comorbid affective disorders and a higher risk for suicide compared with the general population. Epilepsy, depression, and suicidal behavior have been shown to have common pathogenic mechanisms in their etiology. We evaluated the association between epilepsy, suicidal behavior, and depression by using the comprehensive database of all suicides ($n = 1,877$) committed in northern Finland during the years 1988–2002 with information on all hospital-treated somatic and psychiatric disorders. Hospital-treated epilepsy occurred in 1.3% of the victims. Compared with other suicide victims, those with epilepsy were more often female, were older, and had significantly more often suffered from depression. Epilepsy was first diagnosed 8.8 (3.9–11.6) years before suicide, and depression, about 1 year after epilepsy diagnosis. Interictal depression among patients with chronic epilepsy is often classified as atypical or chronic depression, or it can mimic a dysthymic disorder. Therefore, diagnosis and treatment of depression among patients with epilepsy constitute a great challenge in clinical practice.

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## COMMENTARY

In 2003, the United States Agency for Healthcare Research and Quality concluded that there was insufficient evidence

to determine whether patients with refractory epilepsy are at increased risk of suicide (1). A recent meta-analysis reviewed 29 studies with 187 suicides out of a total of 50,814 patients (2). They found that suicide in patients with epilepsy is more frequent than in the general population, but variance in the results, including some cohorts with lower suicide rates for epilepsy patients than for patients with other disorders, limited a definitive conclusion.

Christensen et al. conducted a large population-based, case–control study of 21,169 individuals (492 with epilepsy) who committed suicide from 1980 to 1997 in Denmark. These cases were matched to 423,128 controls in order to assess the association between epilepsy and suicide, controlling for psychiatric, demographic, and socioeconomic factors. They found that suicide was increased over threefold for people with epilepsy and that this increase was still significant after adjusting for psychiatric and socioeconomic factors. The risk of suicide was particularly high in those patients with comorbid psychiatric disease (over 29-fold), although it was high even in those without history of psychiatric diagnosis (almost twofold). The risk was increased for individuals diagnosed in the prior half year (over fivefold) and decreased with increasing duration of epilepsy. The authors did not examine the timing of suicide in relationship to last seizure or to the influence of seizure type, frequency, and severity. In addition, the possible effects of treatments for seizures and depression were not investigated.

In evaluating 1,877 suicides committed in northern Finland from 1988 to 2002, Mainio et al. compared 25 patients with epilepsy treated in the hospital setting to the other 1,852 suicide victims. They found that suicide victims with epilepsy were slightly older (48 vs 43 years old), more likely to have depression (40% vs 19%), and less likely to be under the influence of alcohol at the time of suicide. Diagnosis of epilepsy occurred, on average, 1 year before diagnosis of depression and 8.8 years before suicide. There was an atypically large proportion of patients with generalized (92%) compared with partial (8%) seizure diagnosis, leading the authors to conclude that patients with generalized seizures may be at increased risk. Limitations included the small sample size, lack of patients treated solely as outpatients, and additional factors noted above for the Christensen et al. study.

Depression is a common problem for patients with epilepsy. The prevalence of depression in epilepsy has been reported to range from 3 to 60 percent compared with 2 to 4 percent in the general population (3). The risk of depression is highest for those individuals with refractory epilepsy. The presence of depression is more predictive of a patient's quality of life than seizure frequency and has been linked to increased use of health resources (3,4). Epilepsy is a chronic disorder that impacts psychosocial functioning; thus, one might conclude that depression in epilepsy is simply reactive or situational. The prevalence of depression in epilepsy, however, appears to be higher than depression in other chronic diseases of similar severity. For example, a population-based study of 181,000 individuals found that lifetime prevalence of depression for patients with epilepsy was 29% compared to 17% in diabetes, 16% in asthma, and 8.7% in those without chronic disease (5). In addition, there appears to be a bidirectional relationship between epilepsy and depression (6). Not only is epilepsy a risk factor for depression, but it also appears that depression is a risk factor for epilepsy. In a case–control study of patients with new onset epilepsy in Sweden, patients with epilepsy were found to be seven times more likely to have a history of depression (i.e., preceding the onset of epilepsy) than controls (7). Similarly, elderly patients with new onset epilepsy were four times more likely to have a history of depression prior to epilepsy onset, when compared with controls in a population-based study (8). Another study of children and adults with epilepsy also found that depression was a risk factor and that suicide attempt was an even greater risk factor for subsequent unprovoked seizure (9). It is possible that epilepsy and depression are both symptoms of dysfunction within overlapping neuronal networks (e.g., limbic regions).

Given the relationship of depression to quality-of-life perceptions, healthcare utilization, compliance, and risk of suicide, it would seem appropriate to routinely evaluate epilepsy patients for depression and, when present, consider therapeutic interventions. However, depression in patients with epilepsy is frequently unrecognized and untreated (3,6). In a refractory group of patients undergoing video-EEG monitoring, 50% were depressed and 19% had experienced recent suicidal ideation; however, only 17% of these individuals were being treated with antidepressant medication (6). A survey of randomly selected neurologists from the American Academy of Neurology found that 83% did not routinely screen patients with epilepsy for depression, but 85% of these physicians answered that they would routinely screen if a well-controlled study demonstrated that treatment of depression could improve compliance and quality of life in epilepsy (3).

Factors that contribute to the under-recognition and inadequate treatment of depression for patients with epilepsy include: 1) an apparent lack of appreciation of the common occurrence and impact of depression, 2) the failure to screen or even consider depression as an important issue for clinical care, 3) a lack of well-conducted studies demonstrating the effect of cognitive–behavioral or pharmacological therapies directed at depression, and 4) an increased difficulty in diagnosis because depression in epilepsy appears different or has features that are attributed to the epilepsy itself. For example, depression in epilepsy commonly has an atypical presentation, which may resemble dysthymic disorder and fail to meet DSM-IV diagnostic criteria for depression (6). Dysthymic-like

disorders in epilepsy are characterized by symptoms of irritability and reduced frustration tolerance but fewer symptoms of anhedonia.

How might the rate of suicides be reduced in patients with epilepsy? Although additional research is needed, there are some actions that would seem logical. An awareness of the increased risk of depression and suicide in patients with epilepsy is important for clinicians who care for these patients. Identifying those patients with epilepsy who suffer from depression will allow initiation of treatment interventions for mood disorder and also will assist in identifying those individuals at particular risk for suicide so that preventive measures can be taken.

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