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SPECIAL ARTICLE

Evidence-based guideline update: Vagus nerve stimulation for the treatment of epilepsy

Report of the Guideline Development Subcommittee of the American Academy of Neurology

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ABSTRACT

Objective: To evaluate the evidence since the 1999 assessment regarding efficacy and safety of vagus nerve stimulation (VNS) for epilepsy, currently approved as adjunctive therapy for partial-onset seizures in patients >12 years.

Methods: We reviewed the literature and identified relevant published studies. We classified these studies according to the American Academy of Neurology evidence-based methodology.

Results: VNS is associated with a >50% seizure reduction in 55% (95% confidence interval [CI] 50%–59%) of 470 children with partial or generalized epilepsy (13 Class III studies). VNS is associated with a >50% seizure reduction in 55% (95% CI 46%–64%) of 113 patients with Lennox-Gastaut syndrome (LGS) (4 Class III studies). VNS is associated with an increase in ≥50% seizure frequency reduction rates of ~7% from 1 to 5 years postimplantation (2 Class III studies). VNS is associated with a significant improvement in standard mood scales in 31 adults with epilepsy (2 Class III studies). Infection risk at the VNS implantation site in children is increased relative to that in adults (odds ratio 3.4, 95% CI 1.0–11.2). VNS is possibly effective for seizures (both partial and generalized) in children, for LGS-associated seizures, and for mood problems in adults with epilepsy. VNS may have improved efficacy over time.

Recommendations: VNS may be considered for seizures in children, for LGS-associated seizures, and for improving mood in adults with epilepsy (Level C). VNS may be considered to have improved efficacy over time (Level C). Children should be carefully monitored for site infection after VNS implantation. *Neurology*® 2013;81:1453–1459

GLOSSARY

AAN = American Academy of Neurology; **AE** = adverse effect; **BDI** = Beck Depression Inventory; **CI** = confidence interval; **FDA** = US Food and Drug Administration; **JME** = juvenile myoclonic epilepsy; **LGS** = Lennox-Gastaut syndrome; **SUDEP** = sudden unexpected death in epilepsy; **VNS** = vagus nerve stimulation.

In 1997, the US Food and Drug Administration (FDA) approved vagus nerve stimulation (VNS) as adjunctive therapy for reducing the frequency of seizures in patients >12 years of age with partial-onset seizures refractory to antiepileptic medications.[1] A 1999 American Academy of Neurology (AAN) technology assessment concluded that VNS is indicated for patients >12 years with medically intractable partial seizures who are not candidates for potentially curative surgical resections such as lesionectomies or mesial temporal lobectomies.[2] The authors also recommended that patients undergo a thorough epilepsy evaluation to rule out nonepileptic conditions or treatable symptomatic epilepsies before implantation of a vagus nerve stimulator. At that time, evidence was insufficient to recommend VNS for epilepsy in young children or for seizures associated with Lennox-Gastaut syndrome (LGS). Since the 1999 AAN assessment, the FDA has approved VNS for the adjunctive long-term treatment of chronic or recurrent depression in patients >18 years who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments.[1] Moreover, there are new reports of long-term efficacy and VNS use in pediatric epilepsy and other seizure types and syndromes. We evaluated this evidence using the AAN guideline methodology.

Supplemental data at www.neurology.org

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For this guideline update, we asked the following questions:

1. In children with epilepsy, is using adjunctive VNS therapy for seizure frequency reduction better than not using adjunctive VNS therapy for seizure frequency reduction?
2. In patients with LGS, is using adjunctive VNS therapy for seizure frequency reduction better than not using adjunctive VNS therapy for seizure frequency reduction?
3. In patients with epilepsy, is using VNS associated with mood improvement?
4. In patients with epilepsy, is VNS use associated with reduced seizure frequency over time?
5. In patients undergoing VNS therapy, does rapid stimulation (usual VNS settings are 7 seconds "on" and 30 seconds "off") improve seizure frequency more often than standard stimulation settings (30 seconds "on" and 300 seconds "off")?
6. In patients undergoing VNS therapy, does using additional magnet-activated stimulation trains for auras or at seizure onset interrupt seizures relative to not using additional magnet-induced stimulation trains for auras or at seizure onset?
7. In patients undergoing VNS therapy, have new safety concerns emerged since the last assessment?
8. In children undergoing VNS therapy, do adverse effects (AEs) differ from those in adults?

DESCRIPTION OF THE ANALYTIC PROCESS The AAN Guideline Development Subcommittee convened an expert panel to develop the guideline (appendices e-1 and e-2 on the *Neurology*® Web site at www.neurology.org). We searched MEDLINE, EMBASE, and Web of Science (1996–February 2012) using the key words "seizures," "epilepsy," "mood disorder," "depressive disorder," "vagus nerve stimulation," and "neurostimulation" (appendices e-3–e-5). This search yielded 1,274 abstracts, all of which were reviewed for relevance by at least 2 panel members; 1,058 abstracts were not relevant to provide answers to the questions. Two members then independently reviewed the full text of 216 articles. Articles using the patient as his or her own control were included only if the patient's assessment of seizures (e.g., seizure diary) was independent of the assessing physician's. Therefore, in this update, those articles that used a patient- or parent-maintained seizure diary as an assessment of seizure frequency were deemed as meeting criteria for Class III evidence (see appendix e-6 for classification scheme). Reviews and Class IV reports were excluded, except for case reports of serious safety concerns. Because we found only one article at an evidence level higher than Class III, we cited and included in the evidence tables (see tables e-1 and e-2) Class III articles when more than one of those articles supported a conclusion in response to a question. Some studies included several seizure types and spanned age groups; these were cited in answer to the question appropriate for the majority of the study patients if the specific subset could not be parsed out. All Class III epilepsy and LGS efficacy studies in children were reviewed for AEs, as were Class IV studies that had >50 patients. However, serious AEs are reported herein even if they came from single cases or case series. Retrieved articles did not systematically assess AEs but were descriptive. After study classification, recommendations were linked to evidence strength (appendix e-7).

ANALYSIS OF EVIDENCE **In children with epilepsy, is using adjunctive VNS therapy for seizure frequency reduction better than not using adjunctive VNS therapy for seizure frequency reduction?** Sixteen Class III studies were identified regarding the efficacy of VNS for seizure treatment in children (see table e-1 for study details).[3–18] This group of studies included 2 reports of patients with tuberous sclerosis[16,17] and one report of patients with Dravet syndrome.[18] Ten of 16 studies included subjects through age 18,[3,5,6,8–12,14,15] and one each included subjects up to age 19,[4] age 20,[13,17] age 21,[7] and age 25.[18] One study of 11 patients with tuberous sclerosis had a mean age of 14, and the range of ages included was 2–35, with 2 subjects older than 19 (27 and 35).[16]

Conclusion. Based on data from 14 Class III studies, VNS is possibly effective in achieving >50% seizure frequency reduction (responder rate). In the pooled analysis of 481 children, the responder rate was 55% (95% confidence interval [CI] 51%–59%), but there was significant heterogeneity in the data. Two of the 16 studies[11,13] were not included in the analysis because either they did not provide information about responder rate or they included a significant number (>20%) of adults in their population. The pooled seizure freedom rate was 7% (95% CI 5%–10%).

Recommendation. VNS may be considered as adjunctive treatment for children with partial or generalized epilepsy (Level C).

Clinical context. VNS may be considered a possibly effective option after a child with medication-resistant epilepsy has been declared a poor surgical candidate or has had unsuccessful surgery.

In patients with LGS, is using adjunctive VNS therapy for seizure frequency reduction better than not using adjunctive VNS therapy for seizure frequency reduction? We found 4 Class III studies that evaluated seizures in patients with LGS (table e-1).[19–22] In 2 studies, ages ranged from 5 to 19 years.[19,22] In the third study, the mean age was 13 years (range 4–52), and 18 of 30 subjects were

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younger than 18 years[20]; in the remaining study, the age at the time of implantation was not stated.[21]

Conclusion. Based on data from 4 Class III studies, VNS is possibly effective in achieving >50% seizure frequency reduction in patients with LGS. The pooled analysis of 113 patients with LGS (including data from articles with multiple seizure types where LGS data were parsed out[6,8,9]) yielded a 55% (95% CI 46%–64%) responder rate.

Recommendation. VNS may be considered in patients with LGS (Level C).

Clinical context. The responder rate for patients with LGS does not appear to differ from that of the general population of patients with medication-resistant epilepsy.

In patients with epilepsy, is using VNS associated with mood improvement? Two Class III studies[23,24] showed significant improvements in standard patient-reported mood assessment scales in adult patients with epilepsy when results before implantation were compared with results postimplantation (table e-1). One study evaluated 11 subjects 1, 3, and 6 months postimplantation.[23] Before VNS therapy, 7 of the 11 patients met criteria for "subdepressive mood" by the Montgomery-Åsberg Depression Rating Scale, and the group's mean was within the subdepressive mood range; the mean after VNS was in the nondepressed range. Likewise, 8 of the 11 met criteria for "mild negative symptoms" by the Scale for the Assessment of Negative Symptoms prior to VNS. Scale and subscale scores improved at the study's 3-month follow-up ($p < 0.05$). Mood improvements were sustained at the 6-month follow-up (9 of 11 subjects).

The second study evaluated 20 subjects 3 months postimplantation.[24] Results for change in subject-rated scales by *t* tests showed improvements in the clinician-administered Cornell Dysthymia Rating Scale ($p = 0.001$) and the patient self-report Beck Depression Inventory (BDI) ($p = 0.045$); results on the clinician-administered Hamilton Depression Index (investigator-rated) also significantly improved. The group's mean BDI score pre–VNS treatment was 12.0 ("mild mood disturbance"); this decreased to 9.4 ("nondepressed") post–VNS therapy. Further, BDI scores significantly decreased relative to those for an epilepsy control group (no therapy) studied over the same period (by repeated-measures analysis of variance, $p = 0.07$). This benefit was not correlated with reduced seizure frequency or with stimulation frequency or intensity.

Conclusion. Based on data from 2 Class III studies, VNS is possibly effective for mood improvement in adults with epilepsy.

Recommendation. In adult patients receiving VNS for epilepsy, improvement in mood may be an additional benefit (Level C).

Clinical context. Depression is a common comorbidity for people with epilepsy. VNS may provide an additional benefit by improving mood in some patients; however, the potential for mood improvement should be considered a secondary rather than a primary reason for VNS implantation. The evidence does not clearly support an independent effect on mood in this complex population.

In patients with epilepsy, is VNS use associated with reduced seizure frequency over time? Two Class III studies reported VNS efficacy sequentially for periods greater than 6 months and as long as 12 years (table e-1).[25,26] In these 2 reports of mainly adult subjects with refractory seizures, the proportion of subjects with 50% seizure frequency reduction increased slightly over time. Although the studies did not control for the addition or subtraction of medications over time, making it impossible to assess the effect of the VNS treatment independently, the outcome measure was independently assessed (the subject and the subject's family kept records of seizure occurrence; the investigator did not), so these studies met the criteria for Class III studies.

In one study using data from the vagus nerve stimulator clinical trial involving 440 adult subjects with partial epilepsy,[25] the >50% seizure frequency reduction rates increased by 7% from 1 year to 3 years postimplantation. A ≥50% seizure reduction occurred in 36.8% of patients at 1 year, 43.2% at 2 years, and 42.7% at 3 years. Median seizure reductions relative to baseline were 35% at 1 year, 44.3% at 2 years, and 44.1% at 3 years. In the other study, evaluating 90 patients aged 13–64 with multiple seizure types,[26] the >50% seizure frequency reduction rates increased by 7% from 1 year to 5 years postimplantation. A >50% seizure frequency reduction was reported in 41% at 1 year, 53.2% of 87 patients at 2 years, and 48.9% of 85 patients at 5 years. The effect was described for partial and generalized seizures, with the best response seen in those with generalized tonic–clonic seizures (reduction rates of 70%).

Conclusion. Based on data from 2 Class III studies, VNS is possibly associated with an increase in ≥50% seizure frequency reduction rates of 7% from 1 to 5 years postimplantation.

Recommendation. VNS may be considered progressively effective in patients over multiple years of exposure (Level C).

Clinical context. The loss of medication efficacy over time is a challenging aspect of epilepsy management. The evidence of maintained efficacy in the long term and the trend toward improvement over time make VNS an option.

In patients undergoing VNS therapy, does rapid stimulation (usual VNS settings are 7 seconds "on" and 30 seconds "off") improve seizure frequency more often

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than standard stimulation settings (30 seconds "on" and 300 seconds "off")? In all studies, initial parameters were set at output current 0.25 mA, signal frequency 30 Hz, pulse width 250–500 μs, stimulation "on" time 30 seconds, and stimulation "off" time 300 seconds, with the output current generally increased to 2–3 mA as tolerated.

One Class III article specifically addressed rapid vs standard stimulation settings,[27] evaluating the outcome of 73 adult patients with epilepsy whose optimized settings were either standard stimulation (30 seconds "on" and 300 seconds "off"; n = 41) or rapid stimulation (7 seconds "on" and 30 seconds "off"; n = 32). The standard stimulation group had greater overall seizure frequency reduction than the rapid stimulation group after ~2 years of follow-up. A smaller group of adult patients with epilepsy (reported in the same article), randomized at the onset of VNS treatment to receive standard (n = 14) or rapid (n = 14) stimulation, had no difference in responder rates. However, the authors reported that changing to rapid stimulation several years postimplantation was associated with improvement for several patients.

Two other Class III articles in children[3,8] also showed no consistent improvement with rapid stimulation relative to standard stimulation. In one study,[3] rapid cycling was tried without success in 6 of 46 patients for whom standard VNS cycling had been unsuccessful; of note, "rapid cycling" in this study was defined as less than 148 seconds "off" with no mention of change in "on" time. In the other study,[8] rapid cycling (on-time of 7 seconds, off-time of 12 seconds) was tried in 7 patients who did not have significant seizure reduction after reaching the standard target settings; only 1 of these 7 showed improvement.

Conclusion. These 3 Class III studies were underpowered to detect a difference in efficacy between rapid stimulation (7 seconds "on," 30 seconds "off") used either after standard stimulation (30 seconds "on," 300 seconds "off") was unsuccessful or as an initial treatment setting.

Recommendation. Optimal VNS settings are still unknown, and the evidence is insufficient to support a recommendation for the use of standard stimulation vs rapid stimulation to reduce seizure occurrence (Level U).

Clinical context. Rapid cycling increases the duty cycle and hastens the need for battery replacement; therefore, when used, the efficacy of rapid cycling should be carefully assessed.

In patients undergoing VNS therapy, does using additional magnet-activated stimulation trains for auras or at seizure onset interrupt seizures relative to not using additional magnet-induced stimulation trains for auras or at seizure onset? Five Class III studies[9,28–31] reported on the efficacy of magnet-activated stimulation for auras (simple partial seizures) or seizures.

In the second report using the data from the first double-blind, randomized, controlled study of VNS safety and efficacy (Class III due to retrospective analysis of outcome, which is also confounded by an association with the primary outcome)[28] (E03) in 114 adult subjects with partial epilepsy, 21.3% of the active magnet group reported seizure abortion, whereas 11.9% of the control group (magnet off) reported the same; this difference was nonsignificant. However, response to active magnet use was associated with overall response to VNS treatment (χ^2, $p = 0.0479$).

In another Class III study[29] of 35 patients with partial epilepsy (mean age 30 years, range 10–49 years), 21 were able to self-administer or have a caregiver administer the magnet-activated stimulation and provide reliable magnet-use information. Of these 21, 14 (67%) were able to abort partial or secondary generalized seizures consistently. Eight of these 14 eventually became responders, with a seizure frequency reduction rate of at least 50%.

Another Class III study of 34 patients[30] (mean age 28 years, range 5–70 years) with partial epilepsy showed that of the 12 patients with seizure auras, 8 (67%) could abort the seizure with magnet activation. A fourth Class III study[31] of 34 patients (mean age 30 years, range 16–57 years) reported that 7 patients (22%) could abort seizures by magnet activation during an aura. A fifth Class III study of patients (encephalopathic, mainly pediatric) with drop attacks[9] showed no effect of magnet use; however, this patient population was low functioning and unlikely to communicate about seizure auras reliably.

Conclusion. Based on data from 2 Class III studies, seizure abortion with magnet-activated stimulation is possibly associated with overall response to VNS therapy. Based on 3 Class III studies, magnet-activated stimulation may be expected to abort seizures one-fourth to two-thirds of the time when used during seizure auras (one Class III study omitted because it was not generalizable).

Recommendation. Patients may be counseled that VNS magnet activation may be associated with seizure abortion when used at the time of seizure auras (Level C) and that seizure abortion with magnet use may be associated with overall response to VNS treatment (Level C).

In patients undergoing VNS therapy, have new safety concerns emerged since the last assessment? During the literature review, we identified several case reports regarding complications related to VNS use.[32–40,e1–e11] This information is detailed in table e-3.

Clinical context. Current physician attention to intraoperative rhythm disturbances from VNS use need not

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be changed. The paroxysmal nature of epilepsy poses a challenge for identifying a cardiac rhythm disturbance as device-related rather than as an additional seizure manifestation. Video-EEG and ECG monitoring of new-onset events that might be cardiac-related would be warranted to exclude this possibility in what is likely to be a small number of patients. Reduced sudden unexpected death in epilepsy (SUDEP) rates over time is an important finding associated with VNS therapy; in a cohort of 1,819 individuals followed 3,176.3 person-years from VNS implantation, the SUDEP rate was 5.5 per 1,000 over the first 2 years but only 1.7 per 1,000 thereafter.[e12] The clinical importance of the effect of VNS on sleep apnea and treatment is unclear, but caution regarding VNS use in this setting is suggested.

In children undergoing VNS therapy, do AEs differ from those in adults? In a Class IV study[e13] of 74 children (mean age 8.8 years, range 11 months–18 years) with a minimum follow-up of 1 year and a mean follow-up of 2.2 years, 4 children (5.4%) had the device removed for nonefficacy and intolerance, including symptomatic tachycardia and fever of unknown origin (1 each) and discomfort at the site (2 patients). Infectious surgical complications occurred in 6 (7.1%), including deep infection requiring explantation in 3 (3.6%) and superficial infection treated with oral antibiotics (2 patients) and with IV antibiotics and surgical debridement (1 patient). Two patients experienced electrode fracture, and one had ipsilateral vocal cord paralysis. One patient each reported hoarseness, cough, involuntary arm movement, inappropriate laughter, drooling, torticollis, and urinary retention. One of the 2 electrode fractures was thought to result from the child pulling at the surgical site.

In another Class IV study[e14] of 102 patients (mean age 12 years 3 months, range 21 months–40 years) with only 12 patients aged >18 years, 4 patients (4%) had wound infections. One was treated with IV antibiotics (no explantation); one was treated with IV antibiotics but eventually required explantation even after generator change followed by successful VNS implantation 6 weeks later; one was treated with antibiotics but eventually needed explantation and reimplantation 2 months later; and one was treated with IV antibiotics for an abscess eventually suspected to have resulted from the patient scratching the wound and required device explantation and reimplantation 6 weeks later.

One patient had wound dehiscence from wrestling 9 days postimplantation and was treated with IV and then oral antibiotics. Five patients (5%) had lead fracture. Four of 46 patients who responded to a follow-up questionnaire reported difficulty swallowing during device stimulation.

In another Class IV study[e15] of 69 patients (mean age 10.7 years, range 3–16 years), 3 had wound infection requiring explantation, 2 of whom had reimplantation later. Two with fluid collections around the device were treated with aspiration and antibiotics although the aspirates did not grow organisms. One of these required lead revision. Two other cases had lead fracture. One patient had difficulty swallowing, and one had the VNS turned off due to persistent neck pain. One patient died from unrelated causes.

The clinical trial leading to FDA approval of the VNS device was used for comparison.[e16] It included 254 adult patients with refractory partial epilepsy (mean age 32 years, range 13–60 years). Surgical infectious complications occurred in 3 patients; all were explanted, and one was reimplanted later in the study (time frame unspecified). Left vocal cord paralysis occurred in 2, lower facial muscle paresis occurred in 2, and fluid accumulation over the generator requiring aspiration occurred in one. The frequency of other AEs was "dose"-related; that is, greater at the highest-tolerated stimulation intensity vs the lowest-perceptible stimulation intensity: voice alteration 47.4% vs 9.7%, dyspnea 11.6% vs 1.0%, pharyngitis 15.8% vs 3.9%. Two additional patients discontinued the study due to AEs.

When these adult data were used, infection risk at the VNS site in children (30/764) was increased relative to that in adults (3/254) (odds ratio 3.4 [95% CI 1.0–11.2]).

Clinical context. Children may have greater risk for wound infection than adults due to behaviors more common in children. Extra vigilance in monitoring for occurrence of site infection in children should be undertaken.

RECOMMENDATIONS FOR FUTURE RESEARCH

- More information is needed on the treatment of primary generalized epilepsy in adults. Only one Class II article[e17] addresses this population. The effectiveness of VNS should be studied in epilepsies other than those discussed here, such as primary generalized syndromes. Some reports have discussed VNS use in small numbers of patients with juvenile myoclonic epilepsy (JME); larger reports would help substantiate whether VNS is appropriate in medically refractory JME.
- More information about parameter settings (e.g., cycle time length) would potentially help with better VNS management and use.
- Techniques to reduce infection risk at the VNS site in children should be developed.
- Further information is needed on the effects of VNS on sleep apnea.

AUTHOR CONTRIBUTIONS

George L. Morris III: study concept and design, acquisition of data, analysis or interpretation of data, critical revision of the manuscript for

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important intellectual content, study supervision. David Gloss: analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Jeffrey Buchhalter: analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Kenneth J. Mack: analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Katherine Nickels: analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Cynthia Harden: study concept and design, acquisition of data, analysis or interpretation of data, critical revision of the manuscript for important intellectual content, study supervision.

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DISCLOSURE

G. Morris serves on the speakers bureaus of Eisai, UCB, Cyberonics, Lundbeck, and Pfizer; estimates 5% of his clinical effort is spent on vagus nerve stimulation; and receives research support from Aurora Health Care. D. Gloss reports no disclosures. J. Buchhalter estimates that 25% of his clinical effort is spent on EEG and video-EEG and epilepsy surgery evaluation; serves as a contributing associate editor for *Epilepsy Currents* and *Clinical Neurology News*; and is on the editorial board of *Pediatric Neurology*. K. Mack serves as a Section Editor for *Neurology*®. K. Nickels reports no disclosures. C. Harden serves on the scientific advisory board for UCB and UCB Pregnancy Registry; serves as a journal contributing editor for *Epilepsy Currents*; serves on the speakers bureaus of Pfizer, UCB, and GlaxoSmithKline; and is a consultant for Upsher-Smith. Go to Neurology.org for full disclosures.

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This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. Formal practice recommendations are not intended to replace clinical judgment.

CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. The AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, *Neurology*® peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

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