SPECIAL ARTICLE

Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society

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ABSTRACT

Objective: To determine the incidence rates of sudden unexpected death in epilepsy (SUDEP) in different epilepsy populations and address the question of whether risk factors for SUDEP have been identified.

Methods: Systematic review of evidence; modified Grading Recommendations Assessment, Development, and Evaluation process for developing conclusions; recommendations developed by consensus.

Results: Findings for incidence rates based on 12 Class I studies include the following: SUDEP risk in children with epilepsy (aged 0–17 years) is 0.22/1,000 patient-years (95% confidence interval [CI] 0.16–0.31) (moderate confidence in evidence). SUDEP risk increases in adults to 1.2/1,000 patient-years (95% CI 0.64–2.32) (low confidence in evidence). The major risk factor for SUDEP is the occurrence of generalized tonic-clonic seizures (GTCS); the SUDEP risk increases in association with increasing frequency of GTCS occurrence (high confidence in evidence).

Recommendations: Level B: Clinicians caring for young children with epilepsy should inform parents/guardians that in 1 year, SUDEP typically affects 1 in 4,500 children; therefore, 4,499 of 4,500 children will not be affected. Clinicians should inform adult patients with epilepsy that SUDEP typically affects 1 in 1,000 adults with epilepsy per year; therefore, annually 999 of 1,000 adults will not be affected. For persons with epilepsy who continue to experience GTCS, clinicians should continue to actively manage epilepsy therapies to reduce seizures and SUDEP risk while incorporating patient preferences and weighing the risks and benefits of any new approach. Clinicians should inform persons with epilepsy that seizure freedom, particularly freedom from GTCS, is strongly associated with decreased SUDEP risk. ***Neurology*® 2017;88:1674–1680**

GLOSSARY

AAN = American Academy of Neurology; **AED** = antiepileptic drug; **CI** = confidence interval; **GTCS** = generalized tonic-clonic seizures; **SUDEP** = sudden unexpected death in epilepsy.

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Supplemental data at Neurology.org

This document summarizes information provided in the complete guideline, available at Neurology.org. Appendix e-6, cited in the full guideline (data supplement), is available at Neurology.org.

Sudden unexpected death in epilepsy (SUDEP) is a poorly understood and catastrophic risk of epilepsy. The sensitive nature of discussions of this infrequent but important risk with patients and families has prompted the need for evidence-based information about SUDEP. The goal of this practice guideline is to examine evidence for the SUDEP incidence rate in epilepsy populations and for prognostic factors

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Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on November 7, 2015; by the AAN Practice Committee on January 17, 2016; by the AES Guidelines Committee on November 11, 2016; by the AES Council on Clinical Activities on November 11, 2016; by the AES Executive Committee on November 14, 2016; by the AES Board of Directors on November 30, 2016; and by the AAN Institute Board of Directors on January 11, 2017. This practice guideline was endorsed by the International Child Neurology Association on August 27, 2016.

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for SUDEP occurrence. This in turn will inform an honest and balanced discussion when clinicians counsel people about SUDEP, and provide insight into areas where more clinical research is needed.

Two questions were asked:

1. What is the incidence rate of SUDEP in different epilepsy populations?
2. Are there specific risk factors for SUDEP?

DESCRIPTION OF THE ANALYTIC PROCESS This practice guideline broadly follows the process delineated in the 2004 American Academy of Neurology (AAN) guideline development process manual,[1] with the exception of the processes for formulating conclusions and recommendations, which follow the processes explained in the 2011 AAN guideline development process manual.[2]

In 2010, the AAN Guideline Development, Dissemination, and Implementation Subcommittee and the Guidelines Committee of the American Epilepsy Society convened a panel of experts to develop this practice guideline. The guideline panel engaged an independent medical librarian to search the MEDLINE and Embase databases from earliest available article to November 2010. The panel then performed an identical search in April 2015 to include articles published since November 2010. The keywords for both searches were SUDEP or (sudden and [unexplained or unexpected] and death) combined with the traditional medical subheadings (MeSH) for epilepsy (epilepsy/abnormalities or epilepsy/classification or epilepsy/complications or epilepsy/drug effects or epilepsy/drug therapy or epilepsy/epidemiology or epilepsy/ethnology or epilepsy/etiology or epilepsy/genetics or epilepsy/mortality or epilepsy/physiopathology or epilepsy/prevention and control or epilepsy/therapy) with limits of humans, plus all child: 0–18 years or all adult: 19+ years. Literature types were limited to clinical trial; randomized controlled trial; comparative study; controlled clinical trial; evaluation studies; journal article; multicenter study; research support; NIH, extramural, research support; NIH, intramural, research support; non–US gov't, research support; US gov't, non PHS, research support; or US gov't, PHS, validation studies. Finally, the guideline panel specifically searched causes implicated in SUDEP (i.e., cardiac arrhythmias and preictal autonomic dysfunction), where the hypotheses were tested.

This search yielded 1,068 abstracts, all of which were reviewed for relevance by at least 2 panel members working independently of each other; 744 abstracts were not relevant to provide answers to the questions. Of the remaining 324 abstracts, 2 panel members then obtained the full articles and reviewed them independently for inclusion. Reviewed articles were entered into a database application through an online questionnaire. Seventy articles had data for inclusion, and 254 were excluded because they failed to address the questions, employ an adequate SUDEP definition, or use an appropriate epilepsy comparison group in the prognostic studies. The available literature consisted of multiple Class I articles for incidence, and therefore articles rated Class II or lower were excluded because the Class II publications did not address populations not otherwise encompassed by the Class I articles. Several Class I and multiple Class II articles were available for prognostic questions.

Included articles were required to state that the SUDEP definition provided by Nashef,[3] Annegers,[4] and Leestma et al.[5] was used or to describe criteria in accordance with these definitions. These definitions share the following criteria, and the guideline panel included any article that incorporated these criteria in its SUDEP definition: (1) the patient had epilepsy by reasonable criteria without reference to the criteria used for epilepsy; (2) deaths by drowning, trauma, or status epilepticus were excluded; (3) death could have occurred after a witnessed seizure; (4) other competing causes of death were excluded.

The guideline panel used 2 of the AAN's evidence-based schemes to rate articles: the screening criteria for the incidence question and the prognostic criteria for the risk factor question.

Question 1: What is the incidence of SUDEP in different epilepsy populations? Twelve Class I studies provided incidence rate data.[6–17] Imprecision in study findings resulted in moderate confidence in the evidence for SUDEP rates in childhood and low confidence in the evidence for SUDEP rates in adulthood and overall (table 1). Because of imprecision in the incidence study results with a lack of overlap of 95% confidence interval (CIs) between several comparable study populations, the guideline panel performed a random-effects meta-analysis to provide summary measures of the absolute or relative risk of SUDEP. In addition, to explore reasons for heterogeneity in the absolute risk of SUDEP reported, the panel conducted a meta-analysis of subgroups of studies

Table 1 Conclusions for sudden unexpected death in epilepsy (SUDEP) incidence

Population	SUDEP/1,000 patient-years (confidence interval)	Confidence
Overall	0.58 (0.31–1.08)	Low
Childhood	0.22 (0.16–0.31)	Moderate
Adulthood	1.2 (0.64–2.32)	Low

including different groups of patients with epilepsy (e.g., children vs adults). These meta-analyses have significant unexplained heterogeneity, which may suggest the presence of other unknown or unexplored risk factors.

Rationale for recommendations 1 and 2. Our systematic review found that the SUDEP risk in children with epilepsy is 0.22/1,000 patient-years (95% CI 0.16–0.31). The SUDEP risk increases in adults to 1.2/1,000 patient-years (95% CI 0.64–2.32). There is considerable uncertainty regarding the estimates of the adult risk.

People with epilepsy and their families prefer to be informed of the individual's risk for a catastrophic event such as SUDEP, even when the probability of the event is low.[18] This preference is subject to cultural influences. After being informed of an adverse event, people commonly overestimate the risk of that adverse event happening to them.[19] Such overestimation unduly increases anxiety related to an adverse event. Overestimation can be lessened by presenting the risk as the probability of both having and not having the event,[20] and by using numbers in addition to words[19] and frequencies rather than percentages to convey the risk.[21]

Incidence recommendation 1: SUDEP incidence in children. Clinicians caring for children with epilepsy should inform the children's parents or guardians that (Level B for the following):

1. There is a rare risk of SUDEP.
2. In 1 year, SUDEP typically affects 1 in 4,500 children with epilepsy; in other words, annually, 4,499 of 4,500 children will not be affected by SUDEP.

Incidence recommendation 2: SUDEP incidence in adults. Clinicians should inform adult persons with epilepsy that (Level B for the following):

1. There is a small risk of SUDEP.
2. In 1 year, SUDEP typically affects 1 in 1,000 adults with epilepsy; in other words, annually, 999 of 1,000 adults will not be affected by SUDEP.

Question 2: Are there any risk factors for SUDEP? Six Class I[14,22–26] and 16 Class II articles[6,7,17,23,27–38] provided evidence for this question. Table 2 summarizes the results.

Rationale for recommendation 3. Our systematic review found that a major risk factor for SUDEP is the presence and frequency of generalized tonic-clonic seizures (GTCS). For example, people with 3 or more GTCS per year have a 15-fold increased risk of SUDEP. This relative risk increase translates to an absolute risk of up to 18 deaths per 1,000 patient-years for people with frequent GTCS.[29]

The large SUDEP risk increase from GTCS, coupled with epilepsy monitoring unit evidence[39] demonstrating that a GTCS was always the precipitating event of SUDEP, strongly suggests that GTCS are not just associated with SUDEP but, rather, are in the causal path to SUDEP. From this, it seems reasonable to infer that improved control of an individual's GTCS will result in a reduced risk of SUDEP. Thus, a reduction in SUDEP risk is an additional benefit to the many benefits resulting from improved seizure control.

As with all benefits associated with improved seizure control, the potential benefit of SUDEP risk reduction needs to be balanced with the risks and burdens associated with antiseizure therapies.

Recommendation 3. For persons with epilepsy who continue to experience GTCS, clinicians should continue to actively manage epilepsy therapies to reduce seizure occurrences and the risk of SUDEP while incorporating patient preferences and weighing the risks and benefits of any new approach (Level B).

Rationale for recommendation 4. GTCS are clear risk factors for SUDEP, and nocturnal seizures may also increase risk. These findings, in conjunction with the observation that postictal respiratory depression is a major mechanism in SUDEP,[39] suggest that unwitnessed nocturnal seizures and postictal respiratory depression can cause SUDEP.

Moreover, the presence in the bedroom of another individual at least 10 years of age and of normal intelligence is associated with a decreased SUDEP risk. These results imply that a bedroom observer could detect seizures, check on the patient, and provide sufficient stimulation to prevent respiratory arrest. This association does not indicate that these interventions directly mitigate the mechanism that causes SUDEP.

If it were in accordance with patient and family circumstances and values, nocturnal supervision

Table 2 Conclusions for sudden unexpected death in epilepsy (SUDEP) risk factors

Factor	OR (CI)	Confidence level
Presence of GTCS vs lack of GTCS	10 (17–14)	Moderate
Frequency of GTCS	OR 5.07 (2.94–8.76) for 1–2 GTCS per year and OR 15.46 (9.92–24.10) for >3 GTCS per year	High
Not being seizure-free for 1–5 y	4.7 (1.4–16)	Moderate
Not adding an AED when patients are medically refractory	6 (2–20)	Moderate
Nocturnal supervision (risk reduction)	0.4 (0.2–0.8)	Moderate
Use of nocturnal listening device (risk reduction)	0.1 (0–0.3)	Moderate

Abbreviations: AED = antiepileptic drug; CI = confidence interval; GTCS = generalized tonic-clonic seizure; OR = odds ratio.

could reduce SUDEP risk; however, providing nighttime observation might be overly burdensome and intrusive.

Recommendation 4. For persons with frequent GTCS and nocturnal seizures, clinicians may advise selected patients and families, if permitted by their individualized epilepsy and psychosocial circumstances, to use nocturnal supervision or other nocturnal precautions, such as the use of a remote listening device, to reduce SUDEP risk (Level C).

Rationale for recommendation 5. One of the most consistent findings of this review is that many factors that are indicators of uncontrolled epilepsy, including having GTCS, having frequent GTCS, and the absence of seizure freedom, are strongly associated with SUDEP.

Usually, people with epilepsy and their families prefer to be informed of factors that are associated with an increased risk of a catastrophic event such as SUDEP. Patients are especially interested in factors that might reduce their risk even when a causal link between the factor and a reduction in risk has not been established. Knowledge of these risk factors might suggest behaviors that could modify the risk factors (e.g., improved therapy adherence[40]), increase the person's sense of control, and reduce the anxiety that comes from awareness of the risk. Less severe seizure types, such as focal seizures or myoclonic seizures, are not proven to be associated with increased SUDEP risk, but individuals who have them often remain at risk for GTCS in the setting of therapy nonadherence. Therefore, therapy adherence to maintain freedom from GTCS is important even when an individual is not experiencing this severe seizure type.

Recommendation 5. Clinicians should inform patients with epilepsy that seizure freedom, particularly freedom from GTCS (which is more likely to occur with medication adherence), is strongly associated with a decreased risk of SUDEP (Level B).

Additional conclusions (no recommendations made). The evidence is low that the following factors are associated with altering SUDEP risk:

1. Nocturnal seizures (associated with increased risk)
2. Any specific antiepileptic drug (AED) (none associated specifically with increased risk)
3. Lamotrigine use in women (associated with increased risk)
4. Never having been treated with an AED (associated with increased risk)
5. Number of AEDs used overall (associated with increased risk)
6. Heart rate variability (not associated with increased risk)
7. Extratemporal epilepsy (associated with increased risk)
8. Intellectual disability (associated with increased risk)
9. Male sex (associated with increased risk)
10. Anxiolytic drug use (associated with increased risk)

The evidence is very low or conflicting that the following factors are associated with altering SUDEP risk:

1. Overall seizure frequency when evaluated by using all seizure types
2. Medically refractory epilepsy vs not having well-controlled seizures defined as no seizures in the last year
3. Monotherapy vs polytherapy
4. Carbamazepine, phenytoin, or sodium valproate levels that are above, below, or within the reference range
5. Psychotropic drug use
6. Mental health disorders, lung disorders, or alcohol use
7. Lamotrigine use in people with highly refractory epilepsy
8. Frequent changes in AEDs
9. Therapeutic drug monitoring
10. Undergoing a resective epilepsy surgical procedure (although current research does not rule out the possibility of a beneficial effect or, further, the potential effect of epilepsy surgery on reducing GTCS frequency and epilepsy severity on reducing SUDEP risk)
11. Engel outcome of epilepsy surgery (although current research does not rule out the possibility of a beneficial effect and, further, the potential effect of epilepsy surgery on reducing GTCS frequency and epilepsy severity on reducing SUDEP risk)
12. Vagus nerve stimulator use for more than 2 years (however, current research does not rule out the possibility of a beneficial effect and, further, the potential effect of epilepsy surgery on reducing GTCS frequency and epilepsy severity on reducing the risk of SUDEP)
13. Epilepsy etiology, whether idiopathic or localization-related
14. Structural lesion on MRI
15. Duration of epilepsy
16. Age at epilepsy onset
17. Postictal EEG suppression

SUGGESTIONS FOR FUTURE RESEARCH

1. Systematic methods should be developed to identify and report the incidence of SUDEP in

different epilepsy populations in order to obtain a better understanding of the incidence and causes of this devastating condition.
2. Educational efforts are needed to improve the forensic knowledge of SUDEP among professionals such as medical examiners, coroners, and pathologists in order to help determine, and document on death certificates, the etiology in individuals, and in order to improve overall knowledge of this condition.
3. Research to identify preventable risk factors should be supported and encouraged so that future clinical trials will be conducted to reduce SUDEP occurrence. Of particular importance is to better understand (1) the relationship between the nature, severity, and duration of epilepsy and the occurrence of SUDEP and (2) whether current treatments affect the risk of developing SUDEP.
4. Because of (1) risks identified with frequent GTCS, (2) the fact that one study shows more SUDEP events occur in people in placebo arms of trials, and (3) increased SUDEP risk, serious consideration should be given to avoid assigning people with frequent GTCS to placebo for long periods.

CONFLICT OF INTEREST The American Academy of Neurology and the American Epilepsy Society are committed to producing independent, critical, and truthful practice guidelines. Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this practice guideline. To the extent possible, the AAN and the AES keep separate those who have a financial stake in the success or failure of the products appraised in the practice guidelines and the developers of the practice guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN and AES limit the participation of authors with substantial conflicts of interest. The AAN and the AES forbid commercial participation in, or funding of, practice guidelines projects. Drafts of the practice guidelines have been reviewed by at least 3 AAN committees, at least 1 AES committee, a network of neurologists, *Neurology*® peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at aan.com. For complete information on this process, access the 2004 AAN process manual.[1]

AUTHOR CONTRIBUTIONS

Dr. Harden: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Dr. Tomson: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Gloss: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Buchhalter: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Cross: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Donner: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. French: analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Gil-Nagel: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Hesdorffer: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Smithson: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Spitz: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Walczak: analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Sander: analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Ryvlin: analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

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DISCLOSURE

C. Harden has received royalties from Wiley and UpToDate and has served as a contributing editor for *Epilepsy Currents*. T. Tomson has served as the associate editor of *Epilepsia*; is a member of the editorial boards of *Epilepsy Research*, *Epileptic Disorders*, and the *European Journal of Clinical Pharmacology*; has received honoraria from Sun Pharmaceuticals, UCB, Eisai, and Bial; has served as a member of an expert panel for sudden unexpected death in epilepsy (SUDEP) adjudication in clinical trials of lamotrigine sponsored by GlaxoSmithKline; and has received research support from UCB, GlaxoSmithKline, Bial, Eisai, Novartis, Stockholm County Council, and Citizens United in Research for Epilepsy (CURE). D. Gloss serves as an evidence-based medicine consultant for the American Academy of Neurology (AAN) and has served as an associate editor (risk of bias classification) for *Neurology*®. J. Buchhalter has received funding for travel from the AAN; serves on an editorial advisory board for *Pediatric Neurology* and *Epilepsy Currents*; has served as a consultant to UCB, Upsher-Smith Laboratories, and Eisai; and has performed clinical procedures/imaging studies related to the content of this practice guideline, including EEG and video EEG (25%) and epilepsy surgery evaluation. J. Cross has served as a member of the editorial boards of *Developmental Medicine*, *Child Neurology,* and the *European Journal of Child Neurology*; has a patent for C10 in the treatment of epilepsy; has received royalties for a chapter on childhood epilepsy in *Brain Diseases of the Nervous System* and as editor of *Paediatric Epilepsy*; has received research support from the UK National Institute for Health and Research (NIHR), the European Framework FP7, the Charles Wolfson Foundation, Action Medical Research, and Sparks; and has sat on advisory boards for Vitaflo, Sanofi, Eisai, Viropharma, and Zogenix, for which remuneration is paid to her department. E. Donner has received research support from the Canadian Institutes of Health Research, Dravet Canada, and SUDEP Aware. J. French has served as a consultant for Acorda, Biotie, Eisai Medical Research, GlaxoSmithKline, Impax, Johnson & Johnson, Lewis County General Hospital, Marinus, Novartis, Pfizer, Sunovion, SK Life Science, Supernus Pharmaceuticals, UCB, Upsher-Smith, and Vertex; has received grants from Eisai Medical Research, the US Epilepsy Research Foundation, the Epilepsy Study Consortium, the Epilepsy Therapy Project of the Epilepsy Foundation, Lundbeck, Pfizer, and UCB; and is president of the Epilepsy Study Consortium. All consulting is done on behalf of the Consortium, and fees are paid to the Consortium. New York University receives salary support from the Consortium. A. Gil-Nagel has received personal compensation from Bial, Eisai, GSD Pharma Consulting, UCB Pharma, and Pfizer; has received funding for travel from Bial, Eisai, and GlaxoSmithKline; has served as an editor for *Seizure, Neurologia,* and *Revista de Neurologia*; has served on speakers bureaus for Bial, Eisai, GlaxoSmithKline, and UCB Pharma; and asserts that the information he provides his patients in his epilepsy clinic may be influenced by the results of this practice guideline. D. Hesdorffer is a member of the SUDEP Institute and of the Executive Committee of the North American SUDEP Registry; has served on scientific advisory boards for Upsher-Smith and Acorda; has served as a consultant for Cyberonics; has received funding for travel from the International League Against Epilepsy; has served as an associate editor of *Epilepsia*; has served on the editorial board for *Epilepsy and Behavior*; has served as a contributing editor for *Epilepsy Currents*; and has received funding from the NIH, the Centers for Disease Control and Prevention, the Epilepsy Consortium, the Patient Centered Outcome Research Institute, Finding a Cure for Epilepsy, The Epilepsy Study Consortium, and the Icahn School of Medicine at Mount Sinai (for consulting work on an injury prevention grant). W. Smithson has served on a scientific advisory board for the Sanofi UK consensus guidelines on women with epilepsy, has received travel funding for the Partners Against Mortality in Epilepsy conference on SUDEP (Washington 2016), has received publishing royalties from Blackwell Publishing for the *ABC of Epilepsy*, has received financial support in the form of funding for a general practice research infrastructure from the NIHR (UK), and has given expert witness testimony for the Fatal Accident Inquiry Dundee 2012 (2 cases of SUDEP). M. Spitz has received personal compensation and honoraria for serving on an advisory board for UCB, has received travel funding from Cyberonics (to see the site/factory), has received financial support for a US Department of Defense Study on closed head injury, and has given expert testimony, prepared an affidavit for, and acted as a witness or consultant regarding a legal proceeding. T. Walczak serves on a scientific advisory panel tracking incidence of SUDEP in follow-up of patients treated with the NeuroPace RNS System. Compensation goes directly to his academic department and does not increase his salary. J. Sander is based at University College London/University College London Hospitals, which receives funding from the UK Department of Health's NIHR Biomedical Research Centres; has served on advisory boards for UCB and Eisai; has received speaker honoraria from GlaxoSmithKline, Eisai, UCB, Lundbeck, and Teva; serves on the editorial board of the *Lancet Neurology*; and receives research support from the Dr. Marvin Weil Epilepsy Research Fund, the Epilepsy Society (UK), the Netherlands Epilepsy Fund, Eisai, GlaxoSmithKline, WHO, and EU FP7. His current position is endowed by the Epilepsy Society (UK). P. Ryvlin has served as a chair of the Scientific Advisory Committee for the annual meeting of the French League Against Epilepsy; has received travel funding and honoraria from GlaxoSmithKline, Eisai, Janssen Cilag Pty. Ltd., Cyberonics, Medtronic, and UCB Pharma (in order to participate on industry-funded advisory boards or symposia); has served as a journal editor for *Epilepsia, Epilepsy Research, Epileptic Disorders,* and *Epilepsy Research and Treatment*; has served on speakers bureaus for Eisai, GlaxoSmithKline, and UCB Pharma for a symposium at the European and International Epilepsy Congress (in order to participate on advisory boards or symposia); and has received financial support in the form of a European FP7 grant (EURIPIDES) and grant/research program funding from national (French) entities, including 2 PHRC (Programme Hospitalier de Recherche Clinique), 1 INSERM-DHOS (Institut National de la Santé et de la Recherche Médicale-Direction de l'Hospitalisation et de l'Organisation des Soins) Translationnelle, and 1 Contrat d'Interface INSERM. Go to Neurology.org for full disclosures.

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Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society

Cynthia Harden, Torbjörn Tomson, David Gloss, et al.

Neurology 2017;88;1674-1680
DOI 10.1212/WNL.0000000000003685

Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies

In the article "Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies," Jalini et al. reported atrial cardiopathy in 26.6% of patients meeting the criteria for embolic stroke of unknown source (ESUS) vs 12.1% of patients with large artery atherosclerosis and 16.9% of those with small vessel disease in a cross-sectional study of 846 consecutive patients with ischemic stroke. They also found that patients with ESUS were younger, less hypertensive, and had higher cholesterol and low-density protein levels but fewer left ventricular or atrial abnormalities compared with yet another group with cardioembolism. In response, Drs. Lattanzi and Silvestrini note that they recently found an inverse association between abnormally increased P-wave terminal force in lead V1 (a marker of atrial cardiopathy) and paradoxical or artery-to-artery embolic sources in patients with ESUS. Patients with anterior circulation ESUS more often had ipsilateral (vs contralateral) internal carotid artery plaques with more concerning atherosclerotic findings, whereas younger patients with ESUS had higher incidence of patent foramen ovale (PFO) and lower rates of other vascular risk factors or markers of cardiopathy or atherosclerosis. Stating that ESUS is thus a heterogeneous entity, they encourage the identification of such distinct phenotypes to help guide secondary prevention and potentially targeted interventions. In their reply, the authors agree that the ESUS definition seems too broad and that factors such as PFO, aortic arch, and nonstenotic carotid plaques that were not addressed in their study are important embolic sources in subgroups of patients with ESUS. They note that ongoing trials in subgroups of patients with ESUS will further inform secondary prevention in this population.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
Neurology® 2019;93:978. doi:10.1212/WNL.0000000000008554

Reader response: Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies

Simona Lattanzi (Ancona, Italy) and Mauro Silvestrini (Ancona, Italy)
Neurology® 2019;93:978–979. doi:10.1212/WNL.0000000000008553

We read with great interest the article by Jalini et al.,[1] which demonstrated a higher prevalence of atrial cardiopathy in patients with embolic strokes of undetermined source (ESUS) compared with patients with large artery and small vessel disease strokes.

We recently found that abnormally increased P-wave terminal force in lead V1 in patients with ESUS was inversely associated with paradoxical and artery-to-artery embolic sources, including patent foramen ovale (PFO) and vulnerable, unstable substenotic atherosclerotic plaques of aortic arch and neck arteries.[2] In patients with anterior circulation ESUS, internal carotid artery plaques with increased thickness, mobility, ulceration, and low or heterogeneous echo were more common when ipsilateral rather than contralateral to the stroke site.[3] Younger patients with

Author disclosures are available upon request (journal@neurology.org).

ESUS had lower rates of vascular risk factors, left atrial enlargement, and ventricle dysfunction, but higher incidence of PFO, and no atherosclerosis.[4]

The comprehensive analysis of these alternative causes or putative indicators of embolism according to the presence of atrial cardiopathy would have enhanced the causal link between atrial cardiopathy and stroke occurrence. Far from being a homogeneous entity, the ESUS include a variety of etiologies. The identification of distinct phenotypes on the basis of the underlying pathogenesis could have a great influence in targeting interventions and improving secondary prevention.[5]

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3. Komatsu T, Iguchi Y, Arai A, et al. Large but nonstenotic carotid artery plaque in patients with a history of embolic stroke of undetermined source. Stroke 2018;49:3054–3056.
4. Piffer S, Bignamini V, Rozzanigo U, et al. Different clinical phenotypes of embolic stroke of undetermined source: a subgroup analysis of 86 patients. J Stroke Cerebrovasc Dis 2018;27:3578–3586.
5. Lattanzi S, Brigo F, Cagnetti C, Di Napoli M, Silvestrini M. Patent foramen ovale and cryptogenic stroke or transient ischemic attack: to close or not to close? A systematic review and meta-analysis. Cerebrovasc Dis 2018;45:193–203.

Author response: Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies

Shirin Jalini (Kingston, ON, Canada)
Neurology® 2019;93:979. doi:10.1212/WNL.0000000000008556

We thank Drs. Lattanzi and Silvestrini for their interest in our article.[1] We agree that the current definition of embolic stroke of undetermined source (ESUS) seems too broad and that although we did not address these groups in our study, factors such as PFO, aortic arch, and nonstenotic carotid plaques are important sources of emboli in subpopulations of patients with ESUS. As we have learned repeatedly in stroke research, clinical constructs evolve, and appropriate patient selection can be the key to potentially unmasking therapeutic strategies. We look forward to the results of trials assessing the optimal secondary prevention strategies in subgroups of patients with ESUS.[2,3]

1. Jalini S, Rajalingam R, Nisenbaum R, et al. Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies. Neurology 2019;92:e288–e294.
2. Geisler T, Poli S, Meisner C, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): rationale and study design. Int J Stroke 2017;12:985–990.
3. Kamel H, Longstreth WT Jr, Tirschwell DL, et al. The AtRial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke randomized trial: rationale and methods. Int J Stroke 2019;14:207–214.

Author disclosures are available upon request (journal@neurology.org).

Editors' note: Adherence with psychotherapy and treatment outcomes for psychogenic nonepileptic seizures

In the article "Adherence with psychotherapy and treatment outcomes for psychogenic nonepileptic seizures," Tolchin et al. reported that among 105 participants with documented psychogenic nonepileptic seizures (PNES), adherence with psychotherapy was associated with reduction in PNES frequency, improvement in quality of life, and decrease in emergency department visits at 12–24 months of follow-up. In response, Dr. Sethi notes that psychiatrists and psychologists may be reticent to accept care for patients with PNES when neurologists do not equivocally confirm the diagnosis. He encourages neurologists to sincerely attempt to rule in or rule out coexisting epilepsy in such cases. In their reply, the authors agree that making a definitive diagnosis is possible and that clear communication to both patients and behavioral specialists is essential to facilitate appropriate treatment and adherence. They emphasize the importance of capturing all typical spells on video-electroencephalography and suggest that neurologists review previous EEGs when there is suspicion that a previous "abnormal" EEG may have been overread to avoid clouding an otherwise clear diagnosis of PNES. Dr. Benbadis, who wrote the accompanying editorial for the article, responds in agreement with Dr. Sethi and like the authors notes that only 10%–15% of patients with PNES truly have evidence of coexisting epilepsy. He suggests that including "psychogenic" in the diagnosis is critical, unless there is doubt that there is another nonepileptic diagnosis. He wonders whether mental health professionals may not believe the diagnosis. In addition to encouraging tracking down previous EEGs of concern, he also argues that coexisting epilepsy should not be a reason to deny patients with PNES access to treatment by psychiatrists and psychologists.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
Neurology® 2019;93:980. doi:10.1212/WNL.0000000000008555

Reader response: Adherence with psychotherapy and treatment outcomes for psychogenic nonepileptic seizures

Nitin K. Sethi (New York)
Neurology® 2019;93:980. doi:10.1212/WNL.0000000000008557

I read with interest the article by Tolchin et al. and the accompanying editorial by Dr. Benbadis.[1,2] One reason why psychiatrists and psychologists resist accepting the care of patients with psychogenic nonepileptic seizures (PNES) is the failure of the diagnosing neurologist to confirm the diagnosis unequivocally. Many times, we, as epileptologists, are guilty of saying that the patient has PNES, but—because an EEG in the remote past was read as abnormal—a seizure disorder cannot be ruled out. This creates a diagnostic conundrum and treatment dilemma for both the patient and the psychiatrist. Whenever a diagnosis of PNES is made, we—as neurologists—should make a sincere attempt to rule out or rule in coexisting seizure disorder.

1. Tolchin B, Dworetzky BA, Martino S, Blumenfeld H, Hirsch LJ, Baslet G. Adherence with psychotherapy and treatment outcomes with psychogenic nonepileptic seizures. Neurology 2019;92:e675–e679.
2. Benbadis SR. Psychogenic nonepileptic seizures, conversion, and somatic symptom disorders. Neurology 2019;92:311–312.

Author disclosures are available upon request (journal@neurology.org).

Author response: Adherence with psychotherapy and treatment outcomes for psychogenic nonepileptic seizures

Benjamin Tolchin (New Haven, CT), Barbara A. Dworetzky (Boston), Steve Martino (New Haven, CT), Hal Blumenfeld (New Haven, CT), Lawrence J. Hirsch (New Haven, CT), and Gaston Baslet (Boston)
Neurology® 2019;93:981. doi:10.1212/WNL.0000000000008560

We appreciate Dr. Sethi's important reminder that it is the responsibility of neurologists to diagnose both psychogenic nonepileptic seizures (PNES) and epilepsy and—in cases of PNES—to rule out or rule in comorbid epilepsy. Making as definite a diagnosis is possible and communicating the diagnosis clearly to the patient and to the treating behavioral specialists is essential to the treatment of PNES. An ambiguous diagnosis can undermine the confidence of the patient and behavioral health specialists in the psychotherapeutic process, leading to nonadherence.

This is why it is important, whenever possible, to capture all typical spells on video EEG during spell characterization, as recommended by the International League Against Epilepsy Nonepileptic Seizures Task Force.[1,2] In addition, in situations like those described by Dr. Sethi, in which a previous EEG was read as abnormal, we recommend that the current neurologist obtain and review the original EEG, as normal EEG activity is frequently overread as epileptiform abnormalities.[3] Although comorbid PNES plus epilepsy does exist in a small minority of cases, it is not the common occurrence that older research suggested.[4] It is important that a previous overread EEG not be allowed to confuse an otherwise clear diagnosis of PNES and thereby undermine treatment.

1. Tolchin B, Dworetzky BA, Martino S, Blumenfeld H, Hirsch LJ, Baslet G. Adherence with psychotherapy and treatment outcomes with psychogenic nonepileptic seizures. Neurology Epub 2019 Jan 4.
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3. Benbadis SR. "Just like EKGs!" Should EEGs undergo a confirmatory interpretation by a clinical neurophysiologist? Neurology 2013;80:S47–S51.
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Editorialist response: Adherence with psychotherapy and treatment outcomes for psychogenic nonepileptic seizures

Selim R. Benbadis (Tampa, FL)
Neurology® 2019;93:981–982. doi:10.1212/WNL.0000000000008559

I completely agree with Dr. Sethi that the diagnosis, once made, should be given unequivocally. The diagnosis of psychogenic nonepileptic seizures (PNES) can be challenging at times, but is straightforward most of the time. Similarly, and contrary to higher percentages that are often brought up, only 10%–15% of patients with PNES have evidence for coexisting epilepsy. That means over 85% do not; so, systemically assuming that the patient also has epilepsy is not based on facts. Also vague terms, such as nonepileptic seizures (NES), and ambiguity should be avoided. The "P" is critical. NES and PNES are not the same. Not everything that is nonepileptic is psychogenic. When in doubt, patients should not be labeled psychogenic.

Epilepsy centers always try to rule out coexisting epilepsy. But even if we performed EEG-video monitoring for 6 months, we could not guarantee that the patient will not have an epileptic

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seizure in the seventh month. The concern about coexisting epilepsy may be one reason psychiatrists and psychologists do not want to see those patients, but it is not the main one. I submit that even in patients with unequivocal obvious PNES and no evidence for coexisting epilepsy whatsoever, it is difficult to get them to see psychiatrists and psychologists. More than a concern about coexisting epilepsy, the issue may be that mental health professionals do not believe the diagnosis; worse, some mental health professionals may not believe in the diagnosis of somatic symptom disorders. The issue of a previous EEG that was (mis)read as "showing epilepsy" is frustrating; we must try to obtain the record in question, but that can be difficult. Last, even the 10%–15% of patients with PNES who do have coexisting epilepsy deserve to be treated by psychiatrists and psychologists. That should not be a reason to deny them treatment.

CORRECTIONS

Biallelic variants in *LARS2* and *KARS* cause deafness and (ovario)leukodystrophy

Neurology® 2019;93:982. doi:10.1212/WNL.0000000000007422

In the article "Biallelic variants in *LARS2* and *KARS* cause deafness and (ovario)leukodystrophy" by van der Knaap et al.,[1] first published online ahead of print February 8, 2019, the label for the purple marker in figure 3 should read "Hearing loss/Leukodystrophy." The corrected figure appears in the March 12 issue. The publisher regrets the error.

Reference

1. van der Knaap MS, Bugiani M, Mendes MI, et al. Biallelic variants in *LARS2* and *KARS* cause deafness and (ovario)leukodystrophy. Neurology 2019:92:e1225–e1237.

Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors

Neurology® 2019;93:982. doi:10.1212/WNL.0000000000008565

In the article "Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors" by Harden et al.,[1] the correct value of the lower limit in the confidence interval for the odds ratio of presence of generalized tonic-clonic seizure (GTCS) vs lack of GTCS shown in table 2 is 7. The authors regret the error.

Reference

1. Harden C, Tomson T, Gloss D, et al. Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors. Neurology 2017;88:1674–1680.

Author disclosures are available upon request (journal@neurology.org).

CORRECTIONS

Neuroanatomy of pediatric postoperative cerebellar cognitive affective syndrome and mutism

Neurology® 2020;94:414. doi:10.1212/WNL.0000000000008668

In the editorial "Neuroanatomy of pediatric postoperative cerebellar cognitive affective syndrome and mutism" by Schmahmann,[1] first published online September 16, 2019, Dr. Albazron's last name was misspelled. It appears correctly in the October 15, 2019, issue. The author and the editorial team regret the error.

Reference

1. Schmahmann JD. Neuroanatomy of pediatric postoperative cerebellar cognitive affective syndrome and mutism. Neurology 2019;93:693–694.

A large multicenter study of pediatric myotonic dystrophy type 1 for evidence-based management

Neurology® 2020;94:414. doi:10.1212/WNL.0000000000008819

In the article "A large multicenter study of pediatric myotonic dystrophy type 1 for evidence-based management" by Lagrue et al.,[1] the sentence in "Discussion" (p. e861) should have corresponded with the data in figure 1c and read: "In comparison to previous reports, the observed paternal transmission rate was higher than expected (12.7% in the CF, 42% in the IF, and 68.4% in the JF)." The authors regret the error.

Reference

1. Lagrue E, Dogan C, De Antonio M, et al. A large multicenter study of pediatric myotonic dystrophy type 1 for evidence-based management. Neurology 2019;92:e852–e865.

Self-management program improves participation in patients with neuromuscular disease

A randomized controlled trial

Neurology® 2020;94:414. doi:10.1212/WNL.0000000000008713

In the article "Self-management program improves participation in patients with neuromuscular disease: A randomized controlled trial" by Veenhuizen et al.,[1] first published online September 30, 2019, the affiliations should have read: From the Departments of Rehabilitation (Y.V., E.H.C.C., N.B.M.V., D.M.M., J.T.G., A.C.H.G.) and Neurology (B.G.M.v.E.), Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen; Department of Health Evidence (M.A.J.), Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen; and Rehabilitation Center Klimmendaal (N.B.M.V., B.J.v.K., A.H.), Arnhem, the Netherlands. The affiliations appear correctly in the October 29, 2019, issue. The publisher regrets the error.

Reference

1. Veenhuizen Y, Cup EHC, Jonker MA, et al. Self-management program improves participation in patients with neuromuscular disease: a randomized controlled trial. Neurology 2019;93:e1720–e1731.

