# Practice Parameter: Evaluating an apparent unprovoked first seizure in adults (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society

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SPECIAL ARTICLE

# Practice Parameter: Evaluating an apparent unprovoked first seizure in adults (an evidence-based review)

## Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society

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## ABSTRACT

**Objective:** The Quality Standards Subcommittee of the American Academy of Neurology develops practice parameters as strategies for patient care based on analysis of evidence. For this practice parameter the authors reviewed available evidence relevant to evaluating adults presenting with an apparent unprovoked first seizure.

**Methods:** Relevant questions were defined and addressed by multiple searches of medical literature. Each article was then reviewed, abstracted, and classified using an established evidence scoring system. Conclusions and recommendations were based on a standard three-tiered scheme of evidence classification.

**Results:** For adults presenting with a first seizure, a routine EEG revealed epileptiform abnormalities in approximately 23% of patients, and these were predictive of seizure recurrence. A brain imaging study (CT or MRI) was significantly abnormal in 10% of patients, indicating a possible seizure etiology. Laboratory tests such as blood counts, blood glucose, and electrolyte panels were abnormal in up to 15% of individuals, but abnormalities were minor and did not cause the seizure. Overt clinical signs of infection such as fever typically predicted significant CSF abnormalities on lumbar puncture. Toxicology screening studies were limited, but report some positive tests.

**Recommendations:** EEG should be considered as part of the routine neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure (Level B). Brain imaging with CT or MRI should be considered as part of the routine neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure (Level B). Laboratory tests, such as blood counts, blood glucose, and electrolyte panels (particularly sodium), lumbar puncture, and toxicology screening may be helpful as determined by the specific clinical circumstances based on the history, physical, and neurologic examination, but there are insufficient data to support or refute recommending any of these tests for the routine evaluation of adults presenting with an apparent first unprovoked seizure (Level U). ***Neurology*® 2007;69:1996–2007**

## INTRODUCTION

Seizures are among the most common serious neurologic disorders cared for by neurologists. Annually approximately 150,000 adults will present with a first seizure in the United States.[1] It is estimated that 40 to 50% of these incident seizures recur to be classified as epilepsy, a condition of recurrent unprovoked seizures.[1,2] The lifetime cumulative risk of developing recurrent unprovoked seizures or epilepsy by the age of 80 years ranges from 1.4% to 3.3%.[1] Since even one seizure is a frightening, traumatic event with serious potential consequences, such as loss of driving privileges, limitations for employment, and bodily injury; information about opti-

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mal, evidence-based approaches for evaluating and treating adults presenting with a seizure is important. This practice parameter addresses evidence regarding methods for evaluating a first seizure in adults.

One major study estimates the annual cost of epilepsy in the United States at $12.5 billion in 1995, with the majority of direct cost attributed to diagnostic tests, medical care, and drugs prescribed at the time of the initial evaluation for a seizure disorder or epilepsy.[3] Misdiagnosis may lead to ineffective management choices[4,5] and excessive and unnecessary costs.[3] Errors are not only expensive but may also result in harm to the patient.

Errors in diagnosis, seizure classification, and prognosis are known to lead to inappropriate decisions on the use or choice of antiepileptic drugs and to other serious patient management errors.[4,5] A single seizure can be the first manifestation of epilepsy, which is characterized by recurrent unprovoked seizures (two or more) or may be a symptom of a brain tumor, a systemic disorder, an infection, or a syndrome that deserves special attention and treatment.[6-8]

In this analysis, we focus on the methods and procedures that complement the standard initial history, physical, and neurologic examination. In particular, we assess the yield and value of various diagnostic procedures such as EEG, CT, or MRI, and specific laboratory or diagnostic tests, including blood counts, blood glucose, electrolytes, lumbar puncture, and toxicology screening.[7,9]

For the purposes of this practice parameter, we considered studies of adults (appendix 4), defined here as individuals over 18 years of age. Another recent practice parameter has already addressed evaluation of a first nonfebrile seizure in children.[10]

We attempted to include only patients with an apparent unprovoked first seizure, of any type, and we specifically excluded patients with epilepsy per se. The definition of epilepsy we used requires recurrent (two or more) unprovoked seizures.[6] We defined the first seizure using the International League Against Epilepsy criteria, as did the pediatric guideline,[10] to include a single or multiple seizures within 24 hours with recovery of consciousness between the seizures.[6] We have, therefore, excluded patients who would be diagnosed with epilepsy at the time of initial presentation. However, we recognize that seizures and epilepsy syndromes overlap, may be difficult to separate, and pose similar diagnostic issues, particularly at initial presentation. Studies of individuals presenting with presumed new onset seizures report that about 50% of these individuals, after careful history and questioning, actually have had previous seizures and merit a diagnosis of epilepsy.[11] Although the recurrence rates differ in individuals after a first seizure as opposed to a new diagnosis of epilepsy, both patient groups are at significant risk for seizure recurrence.[2] We also excluded adults presenting with a seizure as a known consequence of an acute condition such as immediate cerebral trauma or stroke.[6] In addition, we considered only patients who had returned to their normal baseline level of function in order to avoid including patients with an acute symptomatic or provoked seizure. We limited our analysis in this manner because these disorders are diagnostically and therapeutically different, but this substantially reduced the number of relevant studies.

## DESCRIPTION OF THE ANALYTICAL PROCESS

This is an evidence-based appraisal of currently available clinical measures pertinent to the initial evaluation of a presumed new unprovoked seizure in adults who have returned to their previous baseline functional levels. The appraisal consists of a systematic review of the literature published in English based on established standards.[12]

Our literature search was conducted by the University of Minnesota using methodology and filters that increase the yield of evidence-based articles. Our search used MedLine, 1966 to November 2004, and also included CINAHL and The Cochrane Trials Register.

All citations and abstracts were printed and screened by two reviewers for any mention of patients with a first seizure, a first presentation, or a new diagnosis of seizure or epilepsy using established criteria (appendix 5). To be included in the review, studies had to report results of any diagnostic or monitoring intervention pertinent to a first or new seizure in adults or adolescents (>18 years of age), with at least 10 patients as total sample size. Studies with mixed

age populations were reviewed for data pertaining to patients >18 years of age when possible.

**Literature search results.** In our search, we found 793 articles and obtained all in abstract form. Each abstract was reviewed by two committee members. We identified 157 articles for review of the full text article (an article was included for review if selected by at least one committee member based on criteria in appendix 4).

These 157 full text articles were obtained and reviewed by two committee members using established criteria. Articles were accepted or rejected when agreed on by both reviewers using inclusion and exclusion criteria in appendix 4. When there was disagreement between the reviewers, a third reviewer cast the determining vote. There were 10 instances of disagreement, resolved by a third party. Of the 157 articles reviewed, 39 were selected as acceptable. An additional 33 studies from the same time period were identified from review articles and other sources; these were subjected to the same process and 14 were selected for inclusion.

Each accepted study was abstracted by one investigator and agreed to by a second. Key data elements sought for extraction from each study included study, patient, and intervention characteristics. In addition, for all diagnostic tests, sensitivity, specificity, and positive and negative predictive value, with its gold standard, were sought. All eligible articles were scored on features pertinent to study design, execution, and reporting, with a range of possible scores as standardized by the American Academy of Neurology Quality Standards Subcommittee.[12]

In order to score the evidence we used the Method of Screening Intervention and Prognosis approved by the Quality Standards Subcommittee (QSS) of the AAN (Appendices 2 and 3).[12] Of the 53 articles, one was ranked as Class I, 11 as Class II, and the remaining 41 as Class III or IV (see appendix E-1 on the *Neurology*® Web site at www.neurology.org).

**Goals of immediate evaluation of a first seizure.** After an adult who presents with a first seizure is stabilized and returns to baseline function, a physician must determine if the event was a seizure; and if so, whether this was the first such event. A history of prior seizures supports a diagnosis of epilepsy and indicates a higher risk for seizure recurrence.[2,10] A careful and complete history, physical, and neurologic examination are critically important at the time of initial presentation. The determination as to whether a seizure occurred is typically based on the history obtained from a reliable observer. The approach in adults is similar to what was presented in the practice parameter for evaluating a first nonfebrile seizure in children,[2] as noted in appendix 5. A good history, physical, and neurologic examination may allow a physician to make the diagnosis of a seizure without additional diagnostic or laboratory testing. However, adults, as well as children, can present with episodic disorders that can be confused with seizures or epilepsy. Such episodic disorders include syncope, migraine, drug reaction or intoxication, and mental disorders such as psychogenic seizures.[5] No single test, clinical finding, or symptom is reliable in discriminating between an initial seizure and such nonepileptic events. In addition, the reliability of witnesses to the event is variable, and witnesses are not always available.

The next goal of assessment is to determine a cause for the seizure. For some patients, the history, physical, and neurologic examination prove adequate to discern a probable cause or provide information to guide the physician to consider other diagnostic testing. Some disorders causing seizures require prompt diagnosis and acute treatment, and others strongly influence prognosis and impact decisions regarding initiation and maintenance of antiepileptic drug therapy. In particular, provoked seizures are the result of acute precipitating disorders such as meningitis, intoxications, trauma, or metabolic derangements including hypoglycemia, and may require prompt intervention to reverse potentially damaging dangerous causes. In contrast, unprovoked seizures may also have causes, but these are not acute precipitating conditions requiring immediate action. Their basis may be cryptogenic (no known cause), remote symptomatic (due to a preexisting brain injury or lesion such as a tumor or stroke), or idiopathic (genetic).[6]

**ANALYSIS OF EVIDENCE** **Electroencephalography.** ***Should an EEG be routinely ordered in an adult presenting with an apparent unprovoked first seizure?*** *Evidence.* Of 1 Class I and 10 Class II articles reviewed (with a total of 1,766 patients) (table 1)[13-24] assessing the yield of EEG, EEGs were reported as abnormal in 12% to 73% (average yield 51%) and reported as significantly abnormal in 8% to 50% (average 29%). The abnormality considered as significant by authors was the presence of epileptiform activity in the form of spikes or sharp waves as interpreted by the local or reading electroencephalographer in patients clinically judged to present with a new onset seizure, evidence similar to that reported for children.[10] This yield is substantial. However, it is also clear from the evidence that a normal EEG does not exclude the presence of a seizure disorder. Indeed, on average about 50% of individuals clinically diagnosed with a seizure have a normal EEG (table 1).

With respect to the value of the EEG as a predictor of risk of seizure recurrence and prognosis, studies support the EEG as useful (table 1). This is similar to findings reported in children.[10] Of the one Class I[13-14] and seven Class II studies[15-21] that consider the EEG as a predictor of risk of seizure recurrence, five studies, a majority, including the only Class I study,[13-15] demonstrate that epileptiform EEG activity in particular generalized spike and wave type discharges or focal spikes are associated

**Table 1** EEG in patients with new onset seizure (Class I and II articles)

| Reference | No. subjects (age, y) | Class | No. studied (%) | No. abnormal (%) | No. sign abnormal (%)* | Duration of follow-up, mo |
|---|---|---|---|---|---|---|
| 17 | 147 (16 and over) | II | 147 (100) | 82 (56) | 51 (35) | 30 to 54 |
| 19 | 76 (mean > 20) | II | 76 (100) | 16 (21) | 12 (16) | 12 to 24 (mean 19) |
| 23 | 56 (16 to 89) | II | 43 (77) | 14 (33) | 8 (19) | NA |
| 16 | 397 (72% over 16) | II | 397 (100) | 221 (56) | 199 (50) | 24 |
| 22 | 107 (17 and over) | II | 103 (96) | 75 (73) | 29 (28) | NA |
| 13, 14 | 173 (70% over 19) | I | 168 (97) | 74 (44) | 13 (8)† | 64 mean (1,990) |
| 18 | 306 (16 and over) | II | 295 (96) | 158 (54) | 79 (27) | 48 |
| 20 | 132 (13 to 86, mean 33) | II | 132 (100) | 59 (45) | 39 (30) | 48 |
| 24 | 91 (15 or older, mean 50) | II | 91 (100) | 63 (69) | 19 (21) | NA |
| 21 | 157 (17 to 84) | II | 157 (100) | 111 (71) | 42 (27) | 24 |
| 15 | 157 (15 to 85, mean 38) | II | 157 (100) | 19 (12) | 19 (12) | 24 |
| Total | 1,799 | | 1,766 (98) | 892 (51) | 510 (29) | |

*Epileptiform activity as interpreted by the local or reading electroencephalographer.
†Significant abnormal is only generalized spike wave.
NA = not applicable or not available.

with a greater risk for seizure recurrence.[13-16,19,21] Therefore the weight of the evidence supports the EEG as of value in predicting seizure recurrence.

What is this degree of increased risk for seizure recurrence associated with epileptiform EEG abnormalities? In the only Class I study, patients with idiopathic seizure disorders and generalized spike wave EEG abnormalities had an actual 55.0% rate of seizure recurrence at 60 months follow-up, while the expected recurrence rate for these patients was calculated in the same study to be less, 48.2%, a small but statistically significant difference.[13,14] A meta-analysis in adults and children by Berg and Shinnar found that individuals with epileptiform EEG abnormalities were more likely to have a seizure recurrence with a pooled relative risk of 2.0 (95% CI = 1.6, 2.6),[2] and this is similar to a more recent study.[16] Our own meta-analysis of the Class I and II studies (table 1) shows similar results, with the estimated post-test probability of a seizure recurrence in patients with epileptiform EEG abnormalities of 49.5% compared to only 27.4% in individuals whose EEGs are completely normal. The data show no significance for other more nonspecific EEG abnormalities, such as focal or diffuse slowing, for predicting seizure recurrence. Several Class III and IV articles are more strongly in support of epileptiform EEG abnormalities as a predictor of seizure recurrence risk.

Some of the study variability in risks for seizure recurrence may relate to the timing of the EEG, time of entry into the clinical study after the initial event, duration of the recording, or treatment with antiepileptic medications. In regard to the timeframe of the EEGs, this was specified in only three studies (table 1)[17,20,24] and varied from within 48 hours[20] to a mean of 15.0 (range 1 to 36) days[24] following the presenting seizure. The effects of antiepileptic drug treatment were specifically considered in one study that carefully randomized treatment; it still found the EEG predictive of seizure recurrence after a first seizure.[16] Furthermore, if there were a treatment bias, we would expect it to be a bias toward demonstrating the EEG as less predictive of seizure recurrence since patients with abnormal EEGs would more likely get treated with antiepileptic drugs that could in turn reduce seizure recurrence.[2]

Studies of patients who presented with a history of previous seizures were excluded in our analysis. It is well described that the EEG is valuable for establishing the nature of a seizure disorder and guiding optimal therapy in such patients or in patients with recurrent seizures or established epilepsy.[2,4,8,25] For example, specific generalized spike wave abnormalities on EEG are noted to be of particular importance in properly diagnosing, determining prognosis, and guiding therapy for patients with juvenile myoclonic epilepsy and absence epilepsy. These types of primary generalized epilepsies are associated with a poor response to some antiepileptic drugs but excellent response to others.[2,4,10,25]

*Conclusion.* For adults presenting with an apparent unprovoked first seizure, analysis of the evidence from 1 Class I and 10 Class II studies indicates that the EEG is probably helpful. It has a

**Table 2** Neuroimaging with CT or MRI in patients with new onset seizure (Class I and II articles)

| Reference | No. subjects (age, y) | Class | Modality | No. studied (%) | No. abnormal (%) | No. sign abnormal (%) |
|---|---|---|---|---|---|---|
| 19 | 100 (mean > 20) | II | CT | 100 (100) | 17 (17) | 17 (17) |
| 23 | 56 (16 to 89) | II | CT | 50 (89) | 14 (28) | 2 (4) |
| 22 | 107 (17 and over) | II | CT and MRI | 45 (42) | 25 (56) | 21 (47) |
| 18 | 408 (16 and over) | II | CT | 375 (92) | 3 (1) | 3 (1) |
| 20 | 132 (13 to 86, mean 33) | II | CT | 85 (64) | 9 (11) | 9 (11) |
| 27 | 132 (adults, mean 46) | II | CT | 119 (90) | 68 (57) | 34 (29) |
| 15 | 157 (15 to 85, mean 38) | II | CT | 154 (98) | 4 (3) | 4 (3) |
| Total | 1,092 | | | 928 (85) | 140 (15) | 90 (10) |

substantial yield with about 29% of EEGs demonstrating significant abnormalities,[25,26] and these abnormalities predict the risk for seizure recurrence. In addition, EEG is regarded as a standard for the initial classification of seizures since it forms a basis for the "clinical and electroencephalographic classification of epileptic seizures."[25,26]

*Recommendations.* 1. The EEG (routine) should be considered as part of the neurodiagnostic evaluation of the adult with an apparent unprovoked first seizure because it has a substantial yield (Level B).[8,25,26]

2. The EEG (routine) should be considered as part of the neurodiagnostic evaluation of the adult with an apparent unprovoked first seizure because it has value in determining the risk for seizure recurrence (Level B).

**Neuroimaging studies.** ***Should a brain imaging study (CT or MRI) be routinely ordered in an adult presenting with an apparent unprovoked first seizure?*** *Evidence.* Of the seven Class II studies[15,18-20,22,23,27] (table 2) that considered the yield and value (with or without contrast agents) of the CT or MRI in adults initially presenting with a seizure (1,092 patients) the CT was reported as abnormal in 1% to 57% (average yield 15%) and was significantly abnormal in 1% to 47% (average 10%). These significant abnormalities affected patient management and included previously unrecognized brain tumors, vascular lesions, and cerebral cysticercosis. Therefore, six studies using CT[15,18-20,23,27] and one using CT and MRI[22] were of value for assessing adult patients with a first seizure. Two of these Class II studies also indicated that the finding of an abnormal CT was associated with a greater risk of seizure recurrence,[18,20] but the other studies did not address this issue. The 13 Class III and 8 Class IV studies of brain imaging we considered further support the value of the CT or MRI in determining a seizure cause.

Interestingly, almost all of the Class II studies report on CT rather than MRI (table 2). One reason for this is that some of the studies are older, but another is that many of these studies are of patients seen acutely in emergency departments, where the CT is the procedure of choice because of the relative speed and ease of obtaining the study and its effectiveness in excluding catastrophic problems that may require immediate attention.[7] MRIs seem to be done in a more selective way, and most of the studies considering MRI are not prospective or well controlled limiting them as Class I or II evidence. However, one MRI study of new onset seizures indicates that the yield of MRI is at least as high and likely higher than CT, but that study was not classified as Class I or II evidence because it included patients with provoked seizures and those presenting after multiple seizures or with pre-existing epilepsy.[28] In general, although these included brain imaging studies varying in their methods and conclusions, the great majority support that neuroimaging can determine potentially important treatable causes of seizures in a significant number of patients, particularly in older patients. A previous QSS study of this issue in children did not recommend neuroimaging as a standard,[10] but our review of studies in adults indicates that neuroimaging deserves greater consideration in adults and particularly in older adults. Not only is the potential to discover significant abnormalities such as tumors greater in adults,[7,28] but the risk associated with MRIs is less since adults are much less likely to require conscious sedation than are children.[10]

A practice parameter from the American Academy of Neurology in 1996 also considered the issue of neuroimaging in the patient presenting with seizures.[29] That study similarly concluded that the decision for neuroimaging and timing of the study should be driven by individual clinical circumstances. In general, when an imaging study is necessary in a non-emergent situa-

**Table 3** Laboratory diagnostic tests in patients with new onset seizure (Class I and II articles)

| Reference | No. subjects (age, y) | Class | Modality | No. studied (%) | No. abnormal (%), 95% CI | No. sign abnormal (%), 95% CI |
|---|---|---|---|---|---|---|
| 23 | 56 (16 to 89) | II | Blood count | 55 (98) | 8 (15), 7.6–26 | 0 (0), 0–6.5 |
| | | | Electrolytes | 55 (98) | 4 (7), 2.9–17.3 | 0 (0), 0–6.5 |
| | | | Glucose | 50 (89) | 5 (10), 4.3–21 | 0 (0), 0–7.1 |
| | | | Calcium | 35 (63) | 0 (0), 0–9.9 | 0 (0), 0–9.9 |
| 18 | 408 (16 and older) | II | Blood count | 371 (91) | NA | 0 (0), 0–1 |
| | | | Electrolytes, calcium | 371 (91) | NA | 0 (0), 0–1 |
| Total | 464 | | | | | |

NA = not available.

tion, MRI is more sensitive and is more likely to show significant abnormalities than is CT.[9,10,29]

*Conclusion.* For adults presenting initially with an apparent unprovoked first seizure, the evidence from seven Class II studies indicates that a brain imaging study, either a CT or MRI, is probably useful. It has a significant yield of about 10%, which may lead to the diagnosis of disorders such as a brain tumor, stroke, cysticercosis, or other structural lesions, and may have some value in determining the risk for seizure recurrence.

*Recommendation.* Brain imaging using CT or MRI should be considered as part of the neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure (Level B).

**Laboratory studies.** Based on review of clinical studies, expert opinion, and position papers, we chose to assess the value of the following laboratory tests: blood glucose, blood counts, electrolytes, lumbar puncture, and toxicology screening in adults with a first seizure.[7,9,18,23,30-32]

***Should blood counts, blood glucose, and electrolyte panels be routinely ordered in an adult with an apparent unprovoked first seizure?*** *Evidence.* Of the two Class II studies[18,23] (464 patients) (table 3) that assessed the yield and value of blood counts, blood glucose, and electrolyte panels, abnormalities were reported in from 0 to 15% for each of these tests, but no clinically significant abnormalities were noted by the authors (table 3). In one Class II study, blood count abnormalities were reported in 15% of patients, but all these were judged by the author to be incidental and clinically insignificant, such as minor increased white blood cell counts that resolved.[23] That same study reported a 10% incidence of hypoglycemia, but again all those abnormalities were judged as mild and clinically insignificant with regard to the seizure. In both the Class II studies, routine electrolytes were obtained in a high percentage of patients, with particular attention to serum calcium and sodium (table 3). Serum calcium was normal in all patients in which it was measured. In one study, sodium abnormalities of hyponatremia were noted in 7% of patients, but, again, all were judged by the author not to be of clinical significance.[23] The other Class II study also reported no significant sodium abnormalities.[18]

There were four Class III studies that showed a higher incidence of significant laboratory abnormalities, particularly for serum sodium and glucose.[30-33] All these studies were based in emergency departments, and the patients were obviously ill with more comorbidities than those in our Class II studies.[18,23] A large proportion were patients with acute symptomatic or provoked rather than apparent unprovoked seizures, as required by our inclusion criteria (appendix 4). Among the reported acute symptomatic causes for the seizures were alcohol withdrawal, acute stroke, tumor, sepsis, or trauma. Also, some studies had many patients with other exclusion criteria (appendix 4) such as focal neurologic deficits, and it was not specified whether patients returned to their normal level of function after the seizure.[30-33] Despite these limitations and acknowledgment that yield is very low,[7] these four Class III studies were consistent in proposing some value to routine screening of blood glucose for hypoglycemia and serum electrolytes for hyponatremia because unanticipated and clinically relevant hypoglycemia and hyponatremia were found in about 1% of these patients.[30-33]

The two Class II studies as well the four Class III we identified do not provide convincing evidence to support or refute significant value for blood glucose, blood count, and electrolytes as routine for adults at initial presentation with epileptic seizures. This finding is similar to the QSS report on initial seizure evaluation in children,[10] and a previous evidence-based analysis.[10]

In general, most studies emphasize that the history and physical examination can guide decision making because they often predict patients who will demonstrate significantly abnormal laboratory tests.[23] For example, patients with persisting altered mental status, fever, or focal neurologic deficits warrant more extensive evaluation and are more likely to have abnormal laboratory findings.[7] A practice parameter from the American College of Emergency Physicians which generally supports our findings still recommends obtaining a blood glucose determination and serum sodium in patients with a first seizure.[7] However, that recommendation was based on evidence from studies that we excluded or downgraded, as our inclusion criteria require, because they involved large numbers of patients with obvious acute symptomatic seizures.

*Conclusion.* Data from two Class II and four Class III studies showed that in adults presenting with an apparent unprovoked first seizure, although some abnormal laboratory results are reported, there is not sufficient evidence to support or refute recommending routine testing of blood glucose, blood counts, or electrolyte panels. The necessity for such studies should be guided by specific clinical circumstances based on the history, physical, and neurologic examination.

*Recommendation.* In the adult initially presenting with an apparent unprovoked first seizure, blood glucose, blood counts, and electrolyte panels (particularly sodium) may be helpful in specific clinical circumstances, but there are insufficient data to support or refute routine recommendation of any of these laboratory tests (Level U).

***Should a lumbar puncture be routinely performed in an adult presenting with an apparent unprovoked first seizure?*** *Evidence.* There were no Class I or II studies, but of the two Class III studies considering the value of a lumbar puncture in patients with a first seizure, both were from emergency departments and reported significant lumbar puncture abnormalities in up to 8% of patients.[30,33] However, not all patients in these two studies had unprovoked seizures or returned to baseline function as our inclusion criteria require. A substantial number had acute symptomatic seizures and level of consciousness was not well specified. Another major limitation of these studies is that lumbar punctures were performed selectively. They were performed in only 68% of the patients in one study[30] and 24% of the other,[33] and this depended on such presenting clinical features as fever or at the discretion of the staff. Consequently, lumbar punctures were not routinely performed, and the decision to perform a lumbar puncture was directed by the clinical history and physical findings. Moreover, in one study the determination of whether the lumbar puncture showed a "significant" abnormality was based largely on whether the patient was admitted to the hospital, rather than whether the test showed a cause for the seizure.[30] In other studies of first seizures that excluded patients with acute symptomatic seizures, lumbar puncture was not considered as an important routine test.[18,23]

In particular, there are no Class I, II or other convincing studies to support a lumbar puncture in patients who are alert, oriented, afebrile, and not immunocompromised.[7] There is some evidence to support a lumbar puncture after a first seizure in patients who are immunocompromised even if they are afebrile.[7,34]

*Conclusion.* Data from two Class III studies revealed significant abnormalities in up to 8% of a mixed group of patients presenting to an emergency department with a first seizure. However, the studies selectively performed lumbar punctures based on clinical findings and included patients who did not meet our inclusion criteria, such as those with acute symptomatic causes for their seizures or who had not returned to their normal baseline function.

*Recommendation.* In the adult initially presenting with an apparent unprovoked first seizure, lumbar puncture may be helpful in specific clinical circumstances, such as patients who are febrile, but there are insufficient data to support or refute recommending routine lumbar puncture (Level U).

***Should toxicologic screening be routinely ordered in an adult presenting with an apparent unprovoked first seizure?*** *Evidence.* Seizures are reported as a consequence of drug intoxication particularly with tricyclic antidepressants, cocaine, and other stimulants.[7,35] In a series of patients with acute medical complications of cocaine intoxication, seizures, often first seizures, accounted for 10% of the presenting symptoms.[36]

Several studies of emergency department admissions for first seizures, including both acute symptomatic and unprovoked seizures, indicated about 3% may relate to drug toxicity or abuse,[7,32,33] and one study advocated toxicology screening for all patients with unexplained first seizures.[30] Still a recent evidence-based review by the American Academy of Emergency Physicians Clinical Policy Committee considering management of adult patients presenting to an emergency department with seizures did not find sufficient evidence in the limited existing prospective or retrospective studies to recommend routine toxicology screening.[7]

In considering this issue, we identified two Class III studies considering the value of toxicology screening in adult patients presenting with a first seizure.[35,36] Although both studies reported some first seizures in patients with abnormal toxicology screening, neither study investigated the use of routine screening in first seizure patients. In addition the studies did not consider mainly unprovoked seizures in which the patient returned to baseline function as our inclusion criteria specify (appendix 4).

*Conclusion.* In two Class III studies considering the value of toxicology screening in adult patients presenting with a seizure, some patients with apparent unprovoked first seizure were included, but neither study investigated the use of routine toxicology screening for such patients.

*Recommendation.* In the adult presenting with an apparent unprovoked seizure, toxicology screening may be helpful in specific clinical circumstances, but there are insufficient data to support or refute a routine recommendation for toxicology screening (Level U).

## CONCLUSIONS AND RECOMMENDATIONS

Diagnosis of seizures, determination of possible causes, classification of seizure type and possible seizure syndrome, and assessment of the risk for recurrence of seizures require timely selection and interpretation of appropriate diagnostic tools including EEGs, CTs or MRIs, blood studies, and lumbar puncture. This report assesses the evidence available to answer the question "What are the most appropriate tools for evaluating a first unprovoked seizure in adults at the time of initial presentation?"

For the adult initially presenting with an apparent unprovoked seizure, diagnostic evaluations influence aspects of patient care and management including drug treatment, patient and family counseling, and the need for immediate hospitalization and subsequent follow-up. This practice parameter reviews the published literature concerning the yield and value of studies following an initial seizure in adults and classifies the strength of available evidence. There is insufficient Class I evidence to provide any recommendation with the highest degree of clinical certainty (see appendix 3). However, there is sufficient Class I and Class II evidence that a routine EEG should be considered as part of the neurodiagnostic evaluation of the adult presenting with an apparent unprovoked first seizure and predicts the risk of seizure recurrence (Level B). There is also sufficient Class II evidence that a brain imaging study, either a CT or MRI, helps determine the presence of a significant abnormality such as a brain tumor. Brain imaging using CT or MRI should be considered as part of the neurodiagnostic evaluation of the adult presenting with a first seizure (Level B). The CT has a major advantage because of the speed with which it can be obtained, so its value is mainly in the emergency situation, but the MRI is regarded by expert opinion as having a higher yield and is the preferable procedure in non-emergency or elective situations.[9,10,29] However, both MRI and CT are of value. The decision to perform other studies including blood glucose, blood counts, electrolyte panels, lumbar puncture, or toxicology screening for the purpose of determining the cause of the seizure or identifying potentially treatable conditions will depend on the specific or individualized clinical circumstances based on the history, physical, and neurologic examination. There are insufficient data to support or refute the use of any one of these tests or procedures as a routine recommendation (Level U).

The history, physical, and neurologic examination are acknowledged by expert consensus to be required for the initial diagnosis and classification of seizures.[26] These standards for the initial diagnosis and classification of seizures form the basis for the "clinical and electroencephalographic classification of epileptic seizures."[21]

Indeed, information from the history, including the type of the seizure,[21] together with findings from the physical and neurologic examination also aid in the determination of a probable cause or risk of recurrence. If the history reveals that there have been other seizures in the past then this indicates epilepsy rather than a single isolated seizure. Although the subsequent diagnostic evaluation may be similar to that for a single unprovoked seizure there are different prognostic and therapeutic implications for a patient with epilepsy.[2,7] Evidence of preexisting seizures provides information for the potential classification of an epilepsy syndrome.[25] Such information is of importance in establishing possible causes, associated comorbidities, prognosis, and optimal treatment of a seizure disorder or epilepsy syndrome.[25,26] Moreover, several features of the clinical history and physical and neurologic examination, such as the presence of specific generalized or focal neurologic deficits, are predictive of higher risks of seizure recurrence.[2,10]

**RECOMMENDATIONS FOR FUTURE RESEARCH** The history, physical, and neurologic examinations form the basis for the diagnosis and

classification of epileptic seizures,[26] and this is acknowledged by expert consensus.[26] Still, future research is warranted to determine the specific aspects of the history, physical, and neurologic examination that are most useful in both initial diagnosis of a seizure and subsequent management. Also, it would be helpful to understand how this type of information should best guide performance and timing of other neurodiagnostic or laboratory studies. An international group recently recommended a broader definition of epilepsy as a brain disorder with a history of at least one seizure and "characterized by an enduring predisposition to generate epileptic seizures."[8] This type of approach will require validation and investigation, including determination of the true value of diagnostic studies such as EEG in establishing the presence of an epileptic syndrome after a first seizure. In regard to the EEG, one limitation of currently available studies is the variability in the timing of the EEG after incident seizure. There is some evidence in children that an EEG done within 24 hours of a presenting seizure gives a higher yield of significant abnormalities.[10]

Although all types of seizures are considered in this analysis, most patients had a convulsive seizure. This may be because convulsive seizures are more likely to prompt acute medical attention than a simple or complex partial seizure. More studies specifically focusing attention on all types of initial seizures, not just convulsive seizures, are needed.

Other factors deserve consideration in future investigations. For instance, the costs of these various tests do not receive much attention in studies of patients with first seizure and should. Also, the elderly are a growing proportion of the general population and warrant special consideration in future investigations. Another unresolved issue relates to the need for immediate hospitalization of patients with a first seizure. Some guidelines exist, but well designed studies are needed.[7]

Prediction of seizure recurrence after a first unprovoked seizure is important to guide decisions regarding antiepileptic drug therapy, patient management, and counseling. Many factors are reported to predict seizure recurrence including the etiology of the seizures and association with neurologic abnormalities.[2] Although the EEG and brain imaging studies are reported to predict seizure recurrence, studies vary in support of that observation and in respect to the specific EEG abnormalities or brain imaging findings that are most significant. Some of this variability regarding EEG findings may relate to the timing of the study after the initial event and to the decision whether to treat with antiepileptic medications. The value of specific findings on the EEG, brain imaging, and other variables deserve further study in regard to seizure recurrence risks. Also, future studies of the clinical utility for such neurodiagnostic procedures should employ standardized tests and prediction algorithms.[37]

Future studies are needed to analyze the value of expert input into the history, physical, neurologic examination, or diagnostic testing such as the EEG or brain imaging. The expertise and qualifications of individuals interpreting such information or tests particularly the EEG or brain imaging vary considerably and may influence interpretations and outcomes.[37] These are not simple "positive" or "negative" tests, like a pregnancy test; they require expertise for proper interpretation. Some other diagnostic studies deserve further analysis in patients presenting with new onset seizures. In particular, routine electrolytes including serum sodium and glucose were reported in some studies to be of value, but this was not consistent or confirmed by other reports. Also, toxicologic screening was reported as important in some limited series, but was not studied in a manner to allow adequate evidence-based verification or refutation of its routine utility.

Studies of patient management and counseling at the time of first diagnosis of a single seizure or epilepsy are recommended. For example, which patients should receive antiepileptic drug treatment, and, if so, exactly what type and when should they get it? Also, when is the patient best advised regarding driving laws and other social issues, and how and by whom should this be done? This is not a trivial issue. For instance, a British study noted that only 21% of all adult first seizure patients received the correct advice about driving limitations.[23]

We recommend that future studies address the issues that we raise here. To best determine how to optimally evaluate the adult presenting with a first seizure, those studies should be structured to emphasize the use of large, well-characterized samples, clearly defined subjects and outcomes, and standardized data collection methods.

**MISSION STATEMENT OF QSS** The mission of the QSS is to prioritize, develop, and publish evidence-based practice parameters related to the diagnosis, treatment, and prognosis of neurologic disorders.

The QSS is committed to using the most rigorous methods available within our budget, in col-

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## APPENDIX 1

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## APPENDIX 2

### AAN classification of evidence for rating of screening article

***Class I:*** A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.

***Class II:*** A statistical, non-referral-clinic-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.

***Class III:*** A sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician.

***Class IV:*** Expert opinion, case reports, or any study not meeting criteria for Class I to III.

## APPENDIX 3

### Classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. (Studies not meeting criteria for Class I–Class III.)

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

## APPENDIX 4

### Exclusion criteria

- Letters and case reports
- Non-English language studies
- Animal studies
- Pharmacodynamic/pharmacokinetic studies
- Studies dealing primarily with established or chronic epilepsy patients
- Studies dealing primarily with acute provoked seizures

### Inclusion criteria

- Study designs: observational (prospective, retrospective, and cross-sectional), or interventional (randomized controlled trials [RCTs], nonrandomized controlled trials [nRCTs], and uncontrolled case series [UCS])
- At least 10 patients, adults, with a first seizure, a first presentation with epilepsy or seizures, or a first diagnosis of epilepsy

- Studies addressing any of the following diagnostic interventions: neuropsychological assessment; imaging with CT, MRI, or PET scans; EEG (standard, video, invasive, ambulatory); lumbar puncture; toxic screens, and laboratory tests (hematology/biochemistry)
- Patients should be over the age of 18 or the study should include a substantial proportion of subjects over the age of 18
- Studies reported in English only
- Studies dealing primarily with apparent unprovoked first seizures

## APPENDIX 5

**Outline for seizure assessment*: Features of a seizure**

*Associated factors*

Age
Medical history – previous history of similar episodes, prior stroke, brain tumor, systemic illness, mental illness, drug or alcohol abuse
Family history
Developmental status
Behavior
Health at seizure onset – febrile, ill, exposed to illness, complaints of not feeling well, sleep deprived
Precipitating events other than illness – trauma, alcohol, medications, illicit drugs, toxins

*Symptoms during seizure (ictal)*

Aura: Subjective sensations
Behavior: Mood or behavioral changes before the seizure
Preictal symptoms: Described by patient or witnessed
Vocal: Cry or gasp, slurring of words, garbled speech
Motor: Head or eye turning, eye deviation, posturing, jerking (rhythmic), stiffening, automatisms (purposeless repetitive movements such as picking at clothing, lip smacking); generalized or focal movements
Respiration: Change in breathing pattern, cessation of breathing, cyanosis
Autonomic: Pupillary dilation, drooling, change in respiratory or heart rate, incontinence, pallor, vomiting
Loss of consciousness or inability to understand or speak

*Symptoms following a seizure (postictal)*

Amnesia for events
Confusion
Lethargy
Sleepiness
Headaches and muscle aches
Transient focal weakness (Todd's paresis)
Nausea or vomiting
Biting of tongue

*Adapted from Hirtz et al.[10]

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# Practice Parameter: Evaluating an apparent unprovoked first seizure in adults (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society

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