

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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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. It is estimated that 40 to 50% of these incident seizures recur to be classified as epilepsy.

This guideline focuses on the methods and procedures that complement the standard initial history, physical, and neurologic examination, particularly the yield and value of:

- Diagnostic procedures such as EEG, CT, or MRI
- Specific laboratory or diagnostic tests, including blood counts, blood glucose, electrolytes, lumbar puncture, and toxicology screening.

This guideline addresses adults over 18 years of age; another AAN guideline addresses first nonfebrile seizures in children.

DESCRIPTION OF THE PROCESS

- To develop a guideline, the AAN poses a question, systematically identifies and evaluates all of the published evidence on the topic, summarizes the evidence in answer to the clinical question, and makes specific recommendations for care.
- 793 article abstracts were identified by searching the MEDLINE and CINAHL databases and Cochrane Library from 1966 – 2004.
- At least two authors reviewed each abstract; 157 relevant articles were obtained.
- At least two authors reviewed each full article; 39 articles met a priori inclusion criteria:
 - Report results of any diagnostic or monitoring interventions pertinent to a first or new seizure in adults or adolescents over 18 years of age
 - Have at least 10 patients as total sample size
- An additional 33 articles were identified from reference lists, review articles and experts; 14 met inclusion criteria.
- Each selected article was evaluated by at least two authors and rated according to the AAN classification of evidence system. Of the 53 articles, one was ranked as Class I, eleven Class II, and the remaining 41 as Class III or IV.
- Conclusions and recommendations were made according to the AAN criteria for translating the quality of the evidence to recommendations.

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.

CLASSIFICATION OF RECOMMENDATIONS

Level A:	Established as effective, ineffective, or harmful for the given condition in the specified population. Level A rating requires at least two consistent Class I studies.*
Level B:	Probably effective, ineffective, or harmful 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.
Level C:	Possibly effective, ineffective, or harmful for the given condition in the specified population. Level C rating requires at least one Class II study or two consistent Class III studies.
Level U:	Data inadequate or conflicting; given current knowledge, treatment 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, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

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.
- 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.
- 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).

CONFLICT OF INTEREST STATEMENT

The American Academy of Neurology is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. The AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guidelines have been reviewed by at least three AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. Disclosure: The authors report no conflicts of interest.

ANALYSIS OF EVIDENCE: EEG

Clinical Question 1: Should an EEG be routinely ordered in an adult presenting with an apparent unprovoked first seizure?

Evidence:

- In one Class I and ten Class II studies, 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.
- The yield is substantial. However, it is also clear from the evidence that a normal EEG does not exclude the presence of a seizure disorder. On average, about 50% of individuals clinically diagnosed with a seizure have a normal EEG (table 1). The data show no significance for other more nonspecific EEG abnormalities, such as focal or diffuse slowing, for predicting seizure recurrence.
- Of the one Class I and seven Class II studies that consider EEG as a predictor of risk, five (including the Class I study) demonstrate that epileptiform EEG activity in particular generalized spike and wave type discharge or focal spikes are associated with a greater risk for seizure recurrence.
- Therefore, the weight of the evidence supports EEG as of value in predicting seizure recurrence.

ANALYSIS OF EVIDENCE: EEG

Clinical Question 2: What is this degree of increased risk for seizure recurrence associated with epileptiform EEG abnormalities?

Evidence:

- In Hauser et al 1982 and 1990 (Class I), 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.
- A meta-analysis in adults and children 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).
- A meta-analysis of Class I and II studies shows 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.
- 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.
- Several Class III and IV articles support that EEG is predictive of seizure recurrence after a first seizure.

Conclusion:

- For adults presenting with an apparent unprovoked first seizure, analysis of the evidence from one Class I and ten Class II studies indicates that the EEG is probably helpful. It has a substantial yield with about 29% of EEGs demonstrating significant abnormalities.

Recommendations:

- A routine EEG 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**).
- A routine EEG 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**).

ANALYSIS OF EVIDENCE: BRAIN IMAGING STUDIES

Clinical Question 3: Should a brain imaging study (CT or MRI) be routinely ordered in an adult presenting with an apparent unprovoked first seizure?

Evidence:

- Seven Class II studies support the value of the CT or MRI in determining a seizure cause.

Table 1: Neuroimaging with CT or MRI in New Onset Seizure Patients

Author(s)	No. Subjects (age in years)	Class	Modality	No. Studied (%)	No. Abn (%)	No. Sign Abn (%)
Das, CP et.al.	100 (mean > 20)	II	CT	100 (100%)	17 (17%)	17 (17%)
Edmondstone	56 (16 to 89)	II	CT	50 (89%)	14 (28%)	2 (4%)
Zetterlund, Fagerlund,)						
Zetterlund	107 (17 and over)	II	CT & MRI	45 (42%)	25 (56%)	21 (47%)
Hopkins, Garman	408 (16 and over)	II	CT	375 (92%)	3 (1%)	3 (1%)
Hui, Tang	132 (13 to 86, mean 33)	II	CT	85 (64%)	9 (11%)	9 (11%)
Schoenenberger, Sabine	132 (adults, mean 46)	II	CT	119 (90%)	68 (57%)	34 (29%)
Van Donselaar, Geerts, Schimsheimer, et. al.	157 (15 to 85, mean 38)	II	CT	154 (98%)	4 (3%)	4 (3%)
Total	1092			928 (85%)	140 (15%)	90 (10%)

Conclusions:

- 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**).

ANALYSIS OF EVIDENCE: LABORATORY STUDIES

Clinical Question 4: Should blood counts, blood glucose, and electrolyte panels be routinely ordered in an adult with an apparent unprovoked first seizure?

Evidence:

- Two Class II studies 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 2).

Table 2: Laboratory Diagnostic Tests in New Onset Seizure Patients (Class I and II articles)

Reference	No. Subjects (age in years)	Class	Modality	No. Studied (%)	No. Abn. (%), 95%CI	# Sign Abn. (%), 95%CI
Edmondstone	56 (16 to 89)	II	Blood count Electrolytes Glucose Calcium	55 (98) 55 (98) 50 (89) 35 (63)	8 (15%) 7.6-26 4 (7%) 2.9-17.3 5 (10%) 4.3-21 0 (0%) 0 – 9.9	0 (0) 0–6.5 0 (0) 0–6.5 0 (0) 0–7.1 0 (0) 0–9.9
Hopkins, Garman, Clarke	408 (16 and older)	II	Blood count Electrolytes, Calcium	371 (91) 371 (91)	NA NA	0 (0) 0-1 0 (0) 0-1
Total	464					

NA=Not available

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 evaluation.

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**).

ANALYSIS OF EVIDENCE: LUMBAR PUNCTURE

Clinical Question 5: Should a lumbar puncture be routinely performed in an adult presenting with an apparent unprovoked first seizure?

Evidence:

- There are no Class I or II studies.
- Two Class III studies from emergency departments reported significant lumbar puncture abnormalities in up to 8% of patients. A substantial number had acute symptomatic seizures and level of consciousness was not well specified.
- Lumbar punctures were performed selectively in only 68% of the patients in one study and 24% of the other; the decision to perform a lumbar puncture was directed by the clinical history and physical findings.
- 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.

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**).

ANALYSIS OF EVIDENCE: TOXICOLOGY SCREENING

Clinical Question 6: Should toxicologic screening be routinely ordered in an adult with an apparent unprovoked first seizure?

Evidence:

- Seizures are reported as a consequence of drug intoxication particularly with tricyclic antidepressants, cocaine, and other stimulants. In a series of patients with acute medical complications of cocaine intoxication, seizures, often first seizures, accounted for 10% of the presenting symptoms.
- 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, and one study advocated toxicology screening for all patients with unexplained first seizures.
- The American Academy of Emergency Physicians Clinical Policy Committee did not find sufficient evidence to recommend routine toxicology screening.
- Two Class III studies reported some first seizures in patients with abnormal toxicology screening, but neither study investigated the use of routine screening in first seizure patients. The studies did not consider mainly unprovoked seizures in which the patient returned to baseline function as our inclusion criteria specify.

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**).

RECOMMENDATIONS FOR FUTURE RESEARCH

- 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. It would be helpful to understand how this type of information should best guide performance and timing of other neurodiagnostic or laboratory studies.
- 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 that an EEG done within 24 hours of a presenting seizure gives a higher yield of significant abnormalities.
- More studies specifically focusing attention on all types of initial seizures, not just convulsive seizures, are needed.
- The costs of the various tests should receive attention.
- 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.
- The value of specific findings on the EEG, brain imaging, and other variables deserve further study in regard to seizure recurrence.
- Future studies of the clinical utility for such neurodiagnostic procedures should employ standardized tests and prediction algorithms.
- 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.
- Studies of patient management and counseling at the time of first diagnosis of a single seizure or epilepsy are recommended.
- Studies should be structured to emphasize the use of large, well-characterized samples, clearly defined subjects and outcomes, and standardized data collection methods.