

ED Seizure and SE Patient Management: Seizure and SE Guidelines Regarding AED Use

Andrew Jagoda, MD



Andrew Jagoda, MD, FACEP

*Professor
Vice Chair for Academic Affairs*

**Department of Emergency Medicine
Mt Sinai College of Medicine and Hospital
New York, NY**

Andrew Jagoda, MD



Disclosures

- Astra Zeneca, NovoNordisk, UCB Pharma Advisory Boards
- Eisai Speakers' Bureau
- Chair, ACEP Clinical Policies Committee
- Executive Board, Brain Attack Coalition
- Executive Board, Foundation for Education and Research in Neurological Emergencies

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Key Clinical Questions

- What are the options and priorities in the treatment of ED seizure and SE patients based on the current clinical policies and guidelines?
- What do the current guidelines recommend regarding which specific 1st or 2nd generation should be used in which ED seizure and SE patients?

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Goals

- Overview of practice guideline development, application, limitations
- Review of the practice guidelines in existence to help determine:
 1. Which patients with a new onset seizures should be started on an AED?
 2. Which patients on AEDs with recurrent seizures should have their AED changed?
 3. Which AED should be used in which patient?

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Seizure Epidemiology in Emergency Medicine

- 1% of adult / 2% of pediatric ED visits
- ED etiologies are often not epilepsy related:
 - Tumor, stroke, trauma
 - Metabolic / toxin, eclampsia
 - Fever in children
- 50,000 – 100,000 ED cases of CSE annually
 - 20% mortality
- 2 million Americans with epilepsy
 - 20 – 30% are not controlled

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Seizure Practice Guidelines

- Treatment of convulsive status epilepticus. Epilepsy Foundation of America. *JAMA* 1993
- Antiepileptic drug prophylaxis in severe traumatic brain injury. *Neurology* 2003
- Clinical Policy: Critical Issues in the evaluation and management. *Ann Emerg Med* 2004
- Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy. *Neurology* 2004
- Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy. *Neurology* 2004

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Why are Clinical Policies Being Written?

- Differentiate “evidence based” practice from “opinion based”
 - Clinical decision making
 - Education
 - Reducing the risk of legal liability for negligence
- Improve quality of health care
 - Assist in diagnostic and therapeutic management
- Improve resource utilization
 - May decrease or increase costs
- Identify areas in need of research

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Interpreting the literature

- Terminology
 - Status epilepticus
- Patient population
 - Children vs adults
- Interventions / outcomes
 - Termination of motor activity vs. termination of electrical activity
 - Seizure recurrence vs morbidity / mortality

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Guideline Development

- Consensus
- Evidence based

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Consensus

- Group of experts assemble
- “Global subjective judgement”
- Recommendations not necessarily supported by scientific evidence
- Limited by bias

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Consensus: Examples

- Calcium, phosphate, and magnesium lab testing in all new onset seizure patients
- Phenytoin to treat alcohol withdrawal seizures
- Phenytoin to prevent late TBI-related seizures

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Evidence Based Guidelines

- Define the clinical question
 - Focused question better than global question
 - Outcome measure must be determined
- Grade the strength of evidence
- Incorporate practice patterns, available expertise, resources and risk benefit ratios
 - External validity

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Description of the Process

- Medical literature search
- Secondary search of references
- Articles graded
- Recommendations based on strength of evidence
- Multi-specialty and peer review

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Description of the Process

Strength of evidence (Class of evidence)

1. **I:** Randomized, double blind interventional studies for therapeutic effectiveness; prospective cohort for diagnostic testing or prognosis
2. **II:** Retrospective cohorts, case control studies, cross-sectional studies
3. **III:** Observational reports; consensus reports

Strength of evidence can be downgraded based on methodological flaws

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Description of the Process

Strength of recommendations:

- **A / Standard:** Reflects a high degree of certainty based on Class I studies
- **B / Guideline:** Moderate clinical certainty based on Class II studies
- **C / Option:** Inconclusive certainty based on Class III evidence

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1. What lab tests are indicated in the otherwise healthy adult patient with a new onset seizure who has returned to a baseline normal neuro status?
2. Which new onset seizure patients who have returned to a normal baseline require neuroimaging in the ED?
3. Which new onset seizure patients who have returned to normal baseline need to be admitted to the hospital and / or started on an AED?

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4. What are effective phenytoin dosing strategies for preventing sz recurrence in patients who present to the ED with a subtherapeutic serum phenytoin level?
5. What agent(s) should be administered to a patient in status who continues to seize despite a loading dose of a benzodiazepine and a phenytoin?
6. When should an EEG be obtained in the ED?

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- Which new onset seizure patients who have returned to normal baseline need to be admitted to the hospital and / or started on an AED?

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Treatment of First Time Seizures

- Coordinated care with neurologist / primary care provider
- Decision to initiate AED treatment depends on the risk of recurrence, ie, etiology
 - Etiology, CT and EEG are the strongest predictors
 - Recurrence risk is up to 20% within the first 24 hours
 - 23% to 71% within 2 years
- Patients needing immediate AED treatment can be loaded with oral or IV phenytoin; IM fosphenytoin; IV valproic acid; IV levetiracetam?
- Decision to admit depends on assessed risk of recurrence, patient compliance, and patients social circumstances

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ACEP 2004: New Onset Sz Rx

- Level A recommendations: None
- Level B recommendations: None
- Level C recommendations:
 - Patients with a normal neurological examination can be discharged from the ED with outpatient follow-up
 - Patients with a normal neurological examination and no co-morbidities and no known structural brain disease do not need to be started on an anti-epileptic drug in the ED.

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Antiepileptic Drug Rx in Severe TBI

- Pooled class I studies demonstrated a significantly lower risk of early post-traumatic seizures in patients given phenytoin prophylaxis compared to controls
- No difference in the risk of late post-traumatic seizures

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Antiepileptic Drug Rx in Severe TBI

- Level A Recommendation: Prophylactic treatment with phenytoin beginning with an IC loading dose should be initiated as soon as possible after injury to decrease the risk of post-traumatic seizures occurring within the first 7 days
- Level B Recommendation: Prophylactic treatment with phenytoin, carbamazepine, or valproate should not routinely be used beyond the first 7 days after injury to decrease the risk of post traumatic seizures occurring beyond that time

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Treatment of New Onset Epilepsy

- Evidence on efficacy, tolerability, and safety of 7 new AEDs reviewed
- Evidence 1987 - 2002
- 23 member review task force
- Two questions:
 - How does the efficacy and tolerability of the new AEDs compare with that of older AEDs in patients with newly diagnosed epilepsy?
 - What is the evidence that the new AEDs are effective in adults or children with primary or secondary generalized epilepsy?

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Reading the Literature

- Placebo controlled trials not possible
- In general studies are not powered to demonstrate superiority of one drug over the other; at best they demonstrate equivalence which is used as a surrogate for effectiveness
- No studies comparing the efficacy and safety of the new AEDs among each other
- There is no literature that addresses the cost benefit related to tolerability and expense of new AEDs over the old

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Treatment of New Onset Epilepsy

- Level A Recommendation: Patients with newly diagnosed epilepsy who require treatment can be initiated on standard AEDs such as carbamazepine, phenytoin, valproic acid, phenobarbital, or on the new AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice of AED will depend on individual patient characteristics
- Level B Recommendation: Lamotrigine can be included in the options for children with newly diagnosed absence seizures

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Treatment of Refractory Epilepsy

- Evidence on efficacy, tolerability, and safety of 7 new AEDs reviewed for the treatment of partial and generalized epilepsies
- Evidence 1987 – 2002
- 23 member review task force

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Treatment of Refractory Epilepsy

- Six questions (3 adult, 3 children):
 - What is the evidence that the new AEDs are effective in refractory partial epilepsy as adjunctive therapy
 - What is the evidence that the new AEDs are effective as monotherapy in refractory partial epilepsy?
 - What is the evidence that the new AEDs are effective for the seizures seen in patients with refractory idiopathic generalized epilepsy?

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Treatment of Refractory Epilepsy: Recommendations

- Level A Recommendation: It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy.
- Level A Recommendation: Oxcarbazepine and topiramate can be used as monotherapy in patients with refractory partial epilepsy.
- Level B Recommendation: Lamotrigine can be used as monotherapy in patients with refractory partial epilepsy
- Level U Recommendation: There is insufficient evidence to recommend use of gabapentin, levetiracetam, tiagabine, or zonisamide in monotherapy for refractory partial epilepsy

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Treatment of Refractory Epilepsy: Recommendations

- Level A Recommendation: topiramate may be used for the treatment of refractory primary generalized tonic clonic seizures in adults and children. There is insufficient evidence for the use of the other new AEDs in this patient group.
- Level A Recommendation: gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures.
- Level A Recommendation: Topiramate and lamotrigine may be used to treat drop attacks associated with the Lennox Gastaut syndrome in adults and children.

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ACEP Clinical Policy

- What agent(s) should be administered to a patient in status who continues to seize despite a loading dose of a benzodiazepine and a phenytoin?

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ACEP 2004: SE Therapeutics

- Level A recommendations: None
- Level B recommendations: None
- Level C recommendations:
 - Administer one of the following agents IV: high dose fosphenytoin or phenytoin, phenobarbital, valproic acid, midazolam infusion, pentobarbital infusion, or propofol infusion

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Conclusions

- Several practice guidelines exist to assist in clinical decision making in the ED management of the patient with seizures
- Evidence based guidelines are limited by the paucity of well designed prospective studies that address relevant management questions
- Care of the seizure patient in the ED requires a collaborative relationship between emergency medicine and neurology

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Questions?

www.FERNE.org

andy.jagoda@mssm.edu

212 241 2987

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