

ED Seizure and SE Patient Management:

A Neurologist's Perspective on Rx Objectives & AED Use

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Key Clinical Questions

- What are the priorities of the neurologist or epileptologist who treats the seizure and epilepsy patients who are seen in follow-up after hospital admission or ED discharge?
- How can the neurologists' priorities be optimally met as emergency physicians diagnose, treat, and document the care of ED seizure and epilepsy patients?

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AAN Guidelines on Seizures and Epilepsy

- Of 94 practice parameters or guidelines of AAN only 3 deal with initiation of AED therapy
 - AED prophylaxis in brain tumors (2000)
 - AED prophylaxis in severe brain injury (2003)
 - Treatment of the child with a first unprovoked seizure (2003)
- No AAN guidelines for prophylaxis with craniotomy
- No AAN guidelines for status epilepticus

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Treatment of the Child With a First Unprovoked Seizure

AAN Practice Parameter

- Treatment with AED is not indicated for the prevention of epilepsy (Level B)
- Treatment with AED may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial side effects (Level B)
- The decision to treat should be individualized and take into account both medical issues and the patient and family preference

Hirtz et al. Neurology 60:166-175, 2003

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AED Prophylaxis in Severe Traumatic Brain Injury

AAN Practice Parameter

- Post-traumatic seizures
 - Prophylaxis with phenytoin warranted in high risk pts to decrease risk of seizures in first 7 days (Level A)
 - Prophylaxis with PHT, CBZ, VPA should not be routinely used beyond the first 7 days to decrease risk of seizures beyond that time (Level B)

Chang and Lowenstein, Neurology 2003; 60:10-16

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AED Prophylaxis in Patients with Newly Diagnosed Brain Tumors

AAN Practice Parameter

- In patients with newly diagnosed brain tumors, anticonvulsant medications are not effective in preventing first seizures. Because of their lack of efficacy and their potential side effects, prophylactic anticonvulsants should not be used routinely in patients with newly diagnosed brain tumors (standard)
- In patients with brain tumors who have not had a seizure, tapering and discontinuing anticonvulsants after the first postoperative week is appropriate, particularly in those patients who are medically stable and who are experiencing side effects (guideline)

Glantz et al. Neurology 2000; 54:1886-1893

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2004 AAN Guideline Summaries for New AEDS

- Released Spring, 2004
- Assessment of new AEDs
 - Newly diagnosed epilepsy
 - Refractory epilepsy
- Guideline is evidence based (Class I - IV)
- Translation of evidence to recommendations – Level A – C
- No comparative data between AEDs

French et al. Neurology 2004; 62:1252-1260, 1261-1273

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Treatment of Epilepsy: Lessons from Pivotal Trials

- Initial VA cooperative trials demonstrated carbamazepine and phenytoin more successful than valproate, phenobarbital, or primidone for partial seizures (Mattson et al. NEJM 1985; 313:145-151)
 - No comparable trials with 2nd generation AEDs
 - Other factors (e.g. pharmacokinetics, enzyme induction) may guide selection

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Treatment of Epilepsy: Lessons from Pivotal Trials

- VA cooperative trial in elderly demonstrated lamotrigine better tolerated than gabapentin and gabapentin better than carbamazepine in new onset seizures
 - Sustained release carbamazepine not used; trial begun before levetiracetam approved


(Rowan AJ et al. Neurology 2005; 64:1868-1873)

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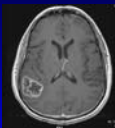
Treatment of Epilepsy: Lessons from Pivotal Trials


- VA status epilepticus trial demonstrated that in convulsive status phenytoin alone not as good as lorazepam or diazepam + phenytoin (Treiman DM et al. *N Engl J Med.* 1998;339:792-798).
- Status trials with valproate difficult to do due to interaction with phenytoin
- No status trials with levetiracetam
 - Animal studies and anecdotal evidence suggest possible efficacy

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Seizure ER Presentation


- New onset seizures
 - Provoked
 - Unprovoked
 - Single or multiple seizures
- Seizures in patient with known seizure history
 - Single or multiple seizures



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Seizure ER Questions: New Onset Seizures

- Provoked seizures often do not require treatment unless multiple
- Assess seizure type
 - Primary generalized typically have onset in childhood or teenage years
 - Almost all unprovoked seizures in adults or elderly are partial onset reflecting symptomatic (or cryptogenic) etiology

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Important Epileptic Syndromes

- Absence epilepsy (childhood or juvenile)
 - May have associated GTCS
- Localization related childhood epilepsies
 - Idiopathic partial (e.g. benign rolandic)
- Juvenile myoclonic epilepsy (JME)
 - Myoclonic seizures, rare GTCS, ± absence
 - Idiopathic

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AED Use: General Considerations

- All AEDs (except ethosuximide) useful for partial seizures (with or without GTCS)
- Broad spectrum AEDs useful for partial and primary generalized seizures
- Some AEDs can exacerbate primary generalized seizures

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AED Use: Initial Monotherapy

- AEDs typically initially approved as adjunctive therapy for partial seizures
- FDA requires superiority trials in epilepsy (not in many other disorders)
 - European union accepts noninferiority trials
 - Superiority trials difficult to do; ethical concerns in refractory patients
- All AEDs probably effective as monotherapy

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Potential AED Exacerbation of Seizures


| | |
|---|---|
| Typical Absence | Myoclonic |
| <ul style="list-style-type: none">• Carbamazepine• Gabapentin• Oxcarbazepine• Phenytoin• Pregabalin• Tiagabine | <ul style="list-style-type: none">• Carbamazepine• Gabapentin• Lamotrigine• Oxcarbazepine• Phenytoin• Pregabalin• Tiagabine |

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Broad Spectrum AEDs

- **First generation**
 - Valproate*
- **Second generation**
 - Lamotrigine
 - Levetiracetam*
 - Topiramate
 - Zonisamide

* Available as parenteral formulations


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Evidence Based Treatment of Idiopathic Generalized Epilepsies

(Class I or II Data Supporting Use)


- **Typical absence**
 - Valproate (FDA approved)
 - Lamotrigine (AAN Guidelines)
- **Myoclonic***
 - Levetiracetam (FDA approved)
- **Generalized tonic-clonic***
 - Topiramate (FDA approved)

*No class I or II data for valproate in primary GTCS myoclonic seizures

Bergey GK, *Epilepsia* 2005; 46 Suppl 9:161-168 Gregory Bergey, MD, FAAN 


Valproate Use in Young Women

- Valproate should not be first choice agent for treatment of seizures in women of childbearing age
 - Major malformation rate of ~10%
 - North American AED registry has identified valproate and phenobarbital as having significantly higher risk to fetus
 - Growing concern about increased risk for learning disabilities

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Treatment Considerations for New Onset Seizures


- Is AED therapy indicated?
 - Risk of seizure recurrence
- Is AED loading indicated?
 - Oral vs parenteral
- Are benzodiazepines indicated?
 - Reserve for status epilepticus or seizure clusters, not just recurrent seizures

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AED Titration

- **AEDs that can be rapidly introduced without respiratory or systemic support**
 - Gabapentin
 - Levetiracetam*
 - Phenytoin / Fosphenytoin*
 - Pregabalin
 - Valproate*

*Agents with approved parenteral formulations

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AED Initiation

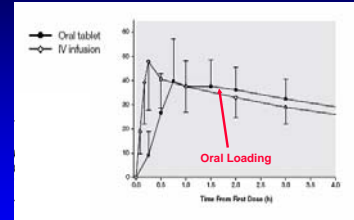
- Steady state is reached after 5 half-lives
 - Agents with short half-lives (e.g. pregabalin, levetiracetam $t_{1/2} \sim 7$ hrs) reach steady state in < 48 hrs
 - Agents with long half lives (e.g. phenobarbital, zonisamide) may take weeks to reach steady state
- Oral loading possible with some AEDs (phenytoin, levetiracetam)

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Levetiracetam: IV and Oral Loading

- Single 1500 mg dose of tablet formulation compared with 15 minute infusion of 1500 mg of IV formulation.
- T_{max} of IV formulation was 0.25 h; for oral formulation was 0.75 h.
- After initial difference in time to peak, plasma concentration vs time curves were comparable for IV and tablet



Ramael S et al. Clin Ther 2006;28:734-744

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Serum Levels and Dose Adjustments

- Therapeutic levels even for first generation agents are somewhat arbitrary
- Therapeutic levels not established for second generation agents
 - Typically sent to outside labs
 - Useful when patient is at upper dose range or noncompliant
 - *Adjustments in dose of 2nd generation AEDs can appropriately be made without levels*

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Serum Levels and Dose Adjustments: Phenytoin

- Range of 10 – 20 $\mu\text{g/ml}$ reasonable target
 - Levels slightly above range provide additional seizure control, but may not be tolerated
 - High levels (~ 40 $\mu\text{g/ml}$) may exacerbate seizures
 - Nonlinear kinetics influence titration
 - Elderly may not tolerate high “therapeutic” levels

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Serum Levels and Dose Adjustments

- Carbamazepine range 4 – 12 $\mu\text{g/ml}$
 - Most patients will not tolerate levels much above this
 - With initiation must go slowly due to autoinduction
- Valproate range 50 - 125 $\mu\text{g/ml}$
 - Patients can tolerate levels above this
 - Dose dependent action tremor
 - Dose dependent thrombocytopenia (platelets functional)

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Serum Levels and Dose Adjustments: 2nd Generation AEDs


- Lamotrigine 3 – 18 $\mu\text{g/ml}$
 - Well tolerated
 - After slow introduction to minimize risk of rash, adjustments well tolerated
 - Enzyme inducers, OCPs, pregnancy dramatically lower levels of LTG
 - Dose range 150 – 800 mg/day as monotherapy

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Serum Levels and Dose Adjustments: 2nd Generation AEDs

- Levetiracetam 10 – 60 µg/ml
 - Adjustments of 500 or 1000 mg well tolerated
 - No induction, no drug interactions
 - Typical dose 1000 – 3000 mg/d; can go higher if benefit

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Serum Levels and Dose Adjustments: 2nd Generation AEDs

- Oxcarbazepine 15 – 50 µg/ml (MHD)
 - Typical daily doses of 600 – 2400 mg, rarely tolerated above this range
 - Less induction and drug reactions than carbamazepine
- Topiramate 3- 20 µg/ml
 - Typical daily doses for epilepsy 100 – 800 mg
 - Titrate slowly at higher doses (> 200 mg)

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Serum Levels and Dose Adjustments: 2nd Generation AEDs

- Pregabalin – no drug levels established
 - Typical daily dose 150 – 600 mg
 - Little benefit with higher dosing
 - No hepatic induction, no drug interactions

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Approach to the ER Patient with Established Seizure Disorder

- Repeat imaging rarely indicated if seizure type/pattern unchanged
- If compliance good dose adjustment of AED appropriate
 - Based on serum levels of 1st generation agents
 - Based on daily dose of 2nd generation agents

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ER Treatment of Epilepsy: Adding a Second AED

- If patient dose not (or would not be expected to) tolerate higher dose of established agent
- Chose agent based on seizure type
 - Partial or primary generalized seizures
 - Partial seizure AED or broad spectrum AED
- Minimize drug interactions
- Choose agent based on patient and side effect profile

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ER Treatment of Epilepsy: Adding a Second AED

- Avoid combinations of phenytoin and carbamazepine (both hepatic inducers)
- Avoid adding carbamazepine to lamotrigine or zonisamide (will reduce levels)
- Avoid adding valproate to lamotrigine (will double levels)

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ER Treatment of Epilepsy: Status Epilepticus

- Phenytoin/fosphenytoin + benzodiazepine still first line therapy
- Do not delay general anesthesia in refractory SE
- Levetiracetam may be useful, but good studies in humans are lacking

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Conclusions

- Seizure classification (partial vs primary generalized) important in AED selection
- 2nd generation AEDs can be adjusted in the ED without serum levels
- Comparative trials between 2nd generation AEDs are needed to guide therapy

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Questions?

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