



A Neurologist's View of Second Generation AEDs: Characteristics, Guidelines and Patient Selection

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Key Clinical Questions

- What are the second generation AEDs, and how do they differ from one another and the first generation AEDs with respect to clinical effectiveness, safety, and ease of use?
- What priorities guide neurologists and epileptologists as they choose AEDs for use in the long-term treatment of epilepsy patients who are diagnosed in the ED?

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Treatment Options of Epilepsy

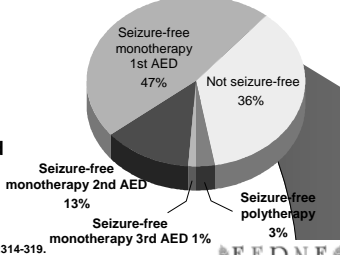
- Antiepileptic drug (AED) - principal treatment
- Epilepsy surgery
- Vagal nerve stimulation
- Ketogenic diet
- Deep brain stimulation


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Success with Antiepileptic Drug Regimens

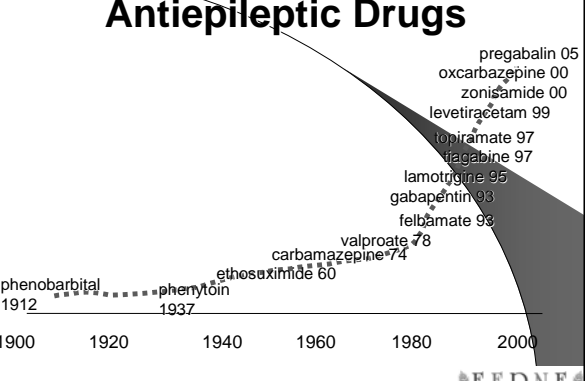
- 63% remained seizure-free
- Seizure-free rates were similar between those treated with monotherapy with an older antiepileptic drug (67%) and those treated with monotherapy with a newer antiepileptic drug (69%)

Previously Untreated Patients (n = 470)




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Antiepileptic Drugs



Year	Drug
1900	phenobarbital
1912	phenobarbital
1937	phenytoin
1937	ethosuximide
1960	ethosuximide
1974	carbamazepine
1978	valproate
1983	felbamate
1993	gabapentin
1995	lamotrigine
1997	tiagabine
1997	topiramate
1999	levetiracetam
2000	zonisamide
2000	oxcarbazepine
2005	pregabalin

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Characteristics of Older AEDs: *Advantages*

- Broad familiarity and long-term experience
 - Known efficacy
 - Lower cost
 - Availability via insurance coverage
- What is old is not necessarily outdated*

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Characteristics of Older AEDs: *Disadvantages*

- Cause hepatic enzyme induction (PB, PHT, CBZ, Primidone) or inhibition (VPA)
- Cause change in internal hormonal compounds (sex steroids, Vit D)
- Produce interaction with commonly used medications (warfarin, oral contraceptives, Ca-channel antagonists, chemotherapy agents)
- Pregnancy Category D

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Advantages of Newer AEDs

- Greater tolerability
- Fewer side effects
- Fewer drug interactions
- Fewer idiosyncratic reactions
- Minimal influence on metabolic pathways
- Pregnancy Category C

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Selecting an Antiepileptic Drug

- Choose antiepileptic drug most suited to the individual patient based on
 - seizure/epilepsy type
 - side effects (anemia, hepatotoxicity, rash, etc.)
 - patient profile (comorbidity, sex, age, etc.)
 - ease of use
 - cost
- Balance between efficacy, tolerability and safety
- Epilepsy may be a lifelong diagnosis – minimize chronic side effects from AEDs (cognitive, reproductive, neuropathy, bone and weight changes, etc.)

Dam M. In: Engel J Jr, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*. Vol 2. Philadelphia, Pa: Lippincott-Raven; 1997:1103-1105.

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Gabapentin (Neurontin)

- Indications: adjunctive therapy for partial seizures in adults and children
- Pharmacokinetics: no liver metabolism, mostly renally excreted
- Doses: adults 300 – 3600 mg/day; children 35 – 80 mg/kg/day
- Drug interactions: none
- Major side effects: somnolence, dizziness, ataxia, weight gain, fatigue

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Lamotrigine (Lamictal)

- Indications: monotherapy for partial and generalized seizures in adults and children; bipolar disorder
- Pharmacokinetics: mostly metabolized by liver
- Doses: depend on concomitant AED (enzyme inducing or inhibiting) and require slow titration; initial dose never exceeds 25 mg/day in adults
- Drug interactions: PHT and CBZ induce metabolism; VPA inhibit metabolism
- Major side effects – Stevens-Johnson syndrome, rash, somnolence, diplopia, ataxia, headache

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Topiramate (Topamax)

- Indications: initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures
- Elimination: mostly by kidney
- Doses: adults - slow titration from 50 - 400 mg/day; children 6 - 9 mg/kg/day
- Drug interactions: increases PHT concentration; reduces effectiveness of oral contraceptives in dose >200 mg/day; concomitant use with VPA may cause hyperammonemia with or w/o encephalopathy
- Side effects: psychomotor slowing, somnolence, weight loss, nephrolithiasis, paresthesia, metabolic acidosis, acute myopia and secondary angle closure glaucoma, oligohidrosis and hyperthermia in children

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Levetiracetam (Keppra)

- Indications: adjunctive therapy for partial onset and for myoclonic seizures in adults and children
- Pharmacokinetics: no liver metabolism; mostly renally excreted
- Doses: adults: 500 - 3000 mg/day; children 40 - 60 mg/kg/day
- Drug interactions - none
- Major side effects – somnolence, fatigue, dizziness, behavioral change

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Levetiracetam (Keppra) – Cont.

- The only second generation of AEDs available for IV injection
- 1:1 conversion from injection to tablets
- Peak plasma concentration reaches in 15 min
- No loading dose is required; the first dose is a therapeutic dose
- Starting dose for injection – 1000 mg/day
- one vial contains 500 mg (500 mg/5 ml)
- must be diluted prior to administration in NaCl 0.9%, Dextrose 5% or Lactate ringer

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Zonisamide (Zonegran)

- Indications: adjunctive therapy for partial and generalized seizures in adults
- Pharmacokinetics: liver metabolism; eliminated primarily by kidneys
- Doses: 100 – 400 mg/day (ones a day)
- Drug interactions - minimal with medications metabolized by P450
- Major side effects – somnolence, dizziness, ataxia, poor appetite and weight loss, nephrolithiasis, fatigue, rash

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Oxcarbazepine (Trileptal)

- Indications: monotherapy in adults or adjunctive therapy in children for partial seizures
- Pharmacokinetics: liver metabolism; eliminated primarily by kidneys
- Doses: adults slow titration from 300 - 2400 mg/day; children 20 - 45 mg/kg/day
- Drug interactions – minimal; reduces effectiveness of oral contraceptives in dose >1200 mg/day
- Major side effects – hyponatremia, somnolence, diplopia, rash, headache, nausea

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Pregabalin (Lyrica)


- Indications: adjunctive therapy for partial seizures in adults
- Pharmacokinetics: no liver metabolism; renally excreted; linear pharmacokinetics
- Doses: 150 – 600 mg/day
- Drug interactions – none
- Major side effects – somnolence, dizziness, dry mouth, peripheral edema, weight gain

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Evidence-based Assessment Guidelines for Prescription of AEDs for Patients with Newly Diagnosed and with Refractory Epilepsy April 2004

- Report of the Therapeutics and Technology Assessment and Quality Standards Subcommittees of the American Academy of Neurology
- Based on 23 expert reviews of 1462 articles published between 1987 and 2003
- Summarizes efficacy, tolerability and safety of seven new AEDs approved by FDA over the last 10 years

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Efficacy and Tolerability of New AEDs in New Onset Seizures as Monotherapy Summary of AAN Subcommittee Report

- Recommendations:
 - Patients with newly diagnosed epilepsy can be initiated on standard AEDs (CBZ, PHT, VPA, PB) or on new AEDs (LTG, OXB, TPM, GBP)
 - LTG can be included in treatment option for children with newly diagnosed absence seizures

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Efficacy of New AED as Adjunctive Therapy in Refractory Partial Epilepsy Summary of AAN Subcommittee Report

- All new AEDs have demonstrated efficacy as add-on therapy and all of them are appropriate as add-on therapy in patients with refractory epilepsy
- For all AEDs slower titration was better tolerated
- All AEDs are more effective in higher doses
- All AEDs side-effects increase in dose-dependent manner

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ILAE Treatment Guidelines Epilepsia, July 2006

- Purpose: To assess which AEDs have the best evidence for long term efficacy as initial monotherapy for adults and children with newly diagnosed epilepsy with different seizure types
- Based on 10 expert reviews of evidence from all applicable articles, 50 RCT and 7 meta-analyses completed over the last 65 years
- All data were divided to 4 classes (I – IV) according to quality of evidence and to 3 levels of efficacy (A - established, B - probably effective and C - possibly effective)

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Summary of Studies and Level of Evidence for Each Seizure Type and Epilepsy Syndrome


Seizure Type or Epilepsy Syndrome	Class I Studies	Class II Studies	Class III Studies	Level of Efficacy and Effectiveness Evidence (in alphabetic order)
Adults with partial-onset seizures	2	1	30	Level A: CBZ, PHT Level B: VPA Level C: GBP, LTG, OXC, PB, TRM, VGB
Children with partial-onset seizures	1	0	17	Level A: OXC Level B: CBZ, PB, PHT, TPM, VPA
Elderly adults with partial-onset seizures	1	1	2	Level A: GBP, LTG Level B: None Level C: CBZ
Adults with generalized-onset tonic-clonic seizures	0	0	23	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA
Children with generalized-onset tonic-clonic seizures	0	0	14	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA
Children with absence seizures	0	0	6	Level A: None Level B: None Level C: ESM, LTG, VPA
Benign epilepsy with centrotemporal spikes (BECTS)	0	0	2	Level A: None Level B: None Level C: CBZ, VPA
Juvenile myoclonic epilepsy (JME)	0	0	0	Level A: None Level B: None Level C: None

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Glaser T, et al. Epilepsia. 2006;47:1094-1120.

ILAE Treatment Guidelines Conclusions

- The absence of comprehensive adverse effects data makes it impossible to develop guideline for the overall optimal initial AED monotherapy
- There is alarming lack of RCT for generalized seizures in children
- Multinational efforts are needed in order to conduct RCT and answer the questions identified in the guideline
- The choice of AED should include efficacy, tolerability, pharmacokinetic and expense

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Summary

- Epilepsy is a common disorder associated with high risk of injury and premature death
- Management of epilepsy focuses on maximizing seizure control and improving the patient's quality of life
- Selection of AED: choose drug most suited to the individual patient based on balance between efficacy, tolerability and safety

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Questions?

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