When to start &

How to select AEDs

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Concepts of medical treatments

Treatment Initiation

- Consider other options if seizures are provoked
- Balance risks between recurrent seizures and adverse events of AEDs
  - Frequency of seizures and risk of recurrent
  - Psychosocial consequences of further seizures
  - Avoid AEDs when diagnosis is in doubt
- AED do not prevent development of epilepsy
- Expectations should be modest (50%)

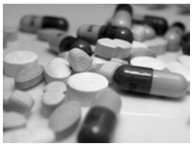
First seizure, evaluate high recurrence risk

- A very high risk of recurrence
  - Examples
    - A single seizure occurring at least a month after a stroke
    - A child with a single seizure conjoined with a structural or remote symptomatic etiology and an epileptiform EEG study
    - A patient in whom diagnosis of a specific epilepsy syndrome associated with persistent threshold alteration can be made after the occurrence of a single seizure
    - A first seizure might present present as status epilepticus

ILAE 2014

Consider (a case-by-case basis)

- Seizure type, syndromic form
- Patient characteristics; age, gender. comorbidities
- Efficacy and side effect profile
- Dosing schedule, drug interaction
- Medical expertise
- Cost, ED drug (national formulary)



Ideal properties for an easy-to-use antiepileptic drug

- Broad spectrum
- High efficacy
- Good tolerability
- No risk of allergic or idiosyncratic reactions including teratogenicity
- Low interaction potential
- Low variability in dosage requirements
- No tolerance
- No withdrawal seizures
- Favorable pharmacokinetics (linear kinetics, T1/2 for 1-2 daily dosing)
- Fast and easy dose escalation rate
- Availability of convenient formulation (syrup, parenteral)
- Low cost, ED

Old (standard) AEDs

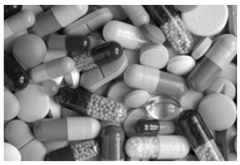
- Phenobarbital
- Phenytoin
- Carbamazepine
- Valproate
- Benzodiazepines

New and newer drugs

- Levetiracetam
- Lamotrigine
- Topiramate
- Gabapentin
- Pregabalin
- Oxcabazepine
- Lacosamide
- Zonisamide
- Vigabatrin
- Felbamate
- Brivaracetam
- Carisbamate
- Eslicarbazepine
- Fluorofelbamate
- Stiripentol
- Ganaxalone
- Retigabine
- Rufinamide
- Perampanel

A new antiepileptic medication

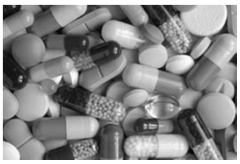
- To change of epileptic drug target
- In poly-therapy: try using multiple actions
- Using in chronic epilepsy (> 5yr)
  - 17%: seizure freedom
  - 25%: seizure 50-99% reduction



French JA, Neurology 2004

A new antiepileptic medication

- Evidence level A
  - Levetiracetam (1,000-3,000 mg/d)
  - Lamotrigine (300-500 mg/d)
  - Topiramate (300-1,000 mg/d)
  - Gabapentin (600-1,800 mg/d)
  - Zonisamide (100-400 mg/d)



French JA, Neurology 2004

Main mechanisms of AEDs

- "A decrease in neuronal excitability"
  - Increased GABAergic
  - Decreased glutamatergic neurotransmission
  - Inhibition of voltage-gated ion channels
  - Modifications of intracellular signaling pathways

Newer medications: drug profiles

- Many mechanism of action (board spectrum)
- Same or better efficacy
- Better drug profile
- Less bound form
- Less side effect
- Less drug interaction

Antiepileptic Drugs and their Molecular Targets

Drug	Sodium Channels	Calcium Channels	GABA System	Glutamate Receptors
Group A (Ion Channel)				
Phenytoin	X			
Carbamazepine	X			
Lamotrigine	X	HVA		
Group B (Mixed Mechanisms)				
Zonisamide	X	T-Type		
Valproate	X	T-Type?	↑ GABA turnover	
Topiramate	X	HVA	$GABA_A$ R	KA/AMPA
Phenobarbital		HVA	$GABA_A$ R	AMPA
Levetiracetam (SV2A)		HVA	?	?
Ethosuximide	?	T-Type		
Group C (GABA-urgic)				
Benzodiazepines			$GABA_A$ R	
Gabapentin		HVA∞28	GABA turnover	
Pregabalin		HVA∞28	GABA turnover	
Vigabatrin			GABA-T	

HVA: high voltage activated

Rogaswski, M., Nat Rev 2004; 5: 1 - 13

Drug	Partial-Onset Seizures	Primary GTC Seizure	Absence Seizure	Myoclonic seizure	Infantile Spasms	Lennox-Gastaut syndrome
Group A (Ion Channel)						
Phenytoin						
Carbamazepine/Oxocarb						
Lamotrigine						
Zonisamide						
Group B (Mixed mechanisms)						
Valproate						
Topiramate						
Phenobarbital						
Benzodiazepines						
Levetiracetam						
Ethosuximide						
Group C(GABA-urgic)						
Gabapentin						
Pregabalin						
Vigabatrin						

Legend

- Efficacy results from randomized controlled trials, generally accepted utility
- Less extensive base of evidence
- Evidence of lack of efficacy or worsening

Rogaswski, M., Nat Rev 2004; 5: 1 - 13

ADVERSE EFFECTS OF AEDs
Early-Onset Adverse Effects

	CBZ	CLB	ETS	GBP	LEV	LTG	OXC	PGN	PB	PHT	TPM	VPA	VGB	ZNS
Somnolence														
Dizziness														
Seizure aggravation														
GI														
Liver failure														
Rash														

- Minimally Increased risk in clinical use
- Risk higher than minimal for AEDs as shown above in clinical use
- Highest risk among AEDs in clinical use

Source: C.E. Elger, D. Schmidt / Epilepsy & Behavior 12 (2008) 501-539

Late-Onset Adverse Effects

	CBZ	CLB	ETS	GBP	LEV	LTG	OXC	PGN	PB	PHT	TPM	VPA	VGB	ZNS
Sedation														
Encephalopathy														
Depression														
Behavioral problems														
Psychotic episodes														
Leukopoenia														
Aplastic anemia														
Thrombopenia														
Megaloblastic anem.														
Pancreatitis														
Nephrolithiasis														
Osteoporosis														
Hyponatremia														
Weight gain														
Weight loss														
Cognition impaired														
Teratogenicity														
Summary	9	8	10	5	3	4	6	4	14	13	9	9	12	9

- Minimally increased risk in clinical use
- Risk higher than minimal for AEDs as shown above in clinical use
- Highest risk among AEDs in clinical use

Source: C.E. Elger, D. Schmidt / Epilepsy & Behavior 12 (2008) 501-539

Therapeutic considerations

- First lines for generalized epilepsy and partial epilepsy
- Partial Seizures:
  - Newer AEDs as efficacious as traditional AEDs (except GBP), but are more tolerable and less enzyme inducing
- Generalized SZs:
  - Vaproic acid, lamotrigine, levetiracetam, topiramate, clobazam
  - Ethosuximide (absence only)
  - GBP, CBZ, OXC, PHT may induce myoclonic seizures

The Treatment of Epilepsy (Simon Shorvon), Third edition, 2009

Epilepsia, 54(3):551–563, 2013
doi: 10.1111/epi.12074

SPECIAL REPORT

Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

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Evidence-Based Guidelines for the Treatment of Epileptic Seizures with AEDs

- Optimal initial monotherapy for patients with newly diagnosed or untreated epilepsy
- ILAE multi-countries Team
  - Epileptologists
  - Clinical pharmacologists
  - Statistician
  - Methodologist

I A prospective, randomized, controlled clinical trial (RCT) or meta-analysis of RCTs, in a representative population that meets all six criteria:
Primary outcome variable: efficacy or effectiveness
Treatment duration: ≥ 48 weeks
Study design: double blind
Design:
For superiority trials: superiority demonstrated
For noninferiority trials or failed superiority trials: the study treatment's efficacy/effectiveness lower limit (95% confidence interval) is above a 20% lower boundary relative to the adequate comparator's point estimate of efficacy/effectiveness using a per-protocol study population (for age/seizure type subgroups).
Study exit: Not forced by a predetermined number of treatment emergent seizures
Appropriate statistical analysis

II An RCT or a meta-analysis meeting all the class I criteria except that
Treatment duration: ≥ 24 weeks but <48 weeks
OR
Design: For noninferiority trials or failed superiority trials: the study treatment's efficacy/effectiveness lower limit (95% confidence interval) is between the 21% and 30% lower boundary relative to the adequate comparator's point estimate of efficacy/effectiveness using a per-protocol study population (for age/seizure type subgroups)

III An RCT or a meta-analysis not meeting the criteria for any class I or class II category. Examples include:
An open-label study
A study with a forced exit criterion
A failed double-blind superiority study, where data from the study's "per-protocol" population (for age/seizure type subgroups) is not provided
A prespecified noninferiority study or a failed double-blind superiority study, where the study treatment's efficacy/effectiveness lower limit (95% confidence interval) is below the 30% lower boundary relative to the adequate comparator's point estimate of efficacy/effectiveness using a per-protocol study population (for age/seizure type subgroups)
For noninferiority studies, lack of using an adequate comparator when one exists

IV Evidence from nonrandomized, prospective, controlled or uncontrolled studies, case series, or expert reports

Table 3. Relationship between clinical trial ratings, level of evidence, and conclusions

Combination(s) of clinical trial ratings	Level of evidence	Condusions
≥ 1 Class I studies or meta-analysis meeting class I criteria sources OR ≥ 2 Class II studies	A	AED established as efficacious or effective as initial monotherapy
1 Class II study or meta-analysis meeting class II criteria	B	AED probably efficacious or effective as initial monotherapy
≥ 2 Class III double-blind or open-label studies	C	AED possibly efficacious or effective as initial monotherapy
1 Class III double-blind or open-label study OR ≥ 1 Class IV clinical studies OR Data from expert committee reports, opinions from experienced clinicians	D	AED potentially efficacious or effective as initial monotherapy
Absence of directly applicable clinical evidence upon which to base a recommendation	E	No data available to assess if AED is effective as initial monotherapy
Positive evidence of lack of efficacy or effectiveness based on class I to IV studies OR Significant risk of seizure aggravation based on class I to IV studies	F	AED established as ineffective or significant risk of seizure aggravation

Recommendation
(Based on efficacy and effectiveness data only)

Evidence Level	Conclusions	Recommendation
A	AED established as efficacious or effective as initial monotherapy	First line monotherapy
B	AED probably efficacious or effective as initial monotherapy	First line monotherapy
C	AED possibly efficacious or effective as initial monotherapy -	Alternative first line monotherapy
D	AED potentially efficacious or effective as initial monotherapy	Weak efficacy
E	No data available to assess if AED is effective as initial monotherapy	No data
F	AED established as ineffective or significant risk of seizure aggravation	Should not be used for initial monotherapy

AEDs for

- Adults with partial-onset seizures
- Elderly with partial-onset seizures
- Adults with generalized-onset tonic-clonic seizures
- JME

Optimal initial monotherapy for patients with newly diagnosed or untreated epilepsy

Partial Seizures: Adults recommendations

Level	AEDs
A	**CBZ, PHT, LEV, ZNS**
B	**VPA**
C	**GBP, LTG, OXC, PB, TPM, VGB**
D	CZP, PRM
E	Others
F	None

Optimal initial monotherapy for patients with newly diagnosed or untreated epilepsy

Partial Seizures: Elderly recommendations

Level	AEDs
A	**GBP, LTG**
B	**None**
C	**CBZ**
D	TPM, VPA
E	Others
F	None

Optimal initial monotherapy for patients with newly diagnosed or untreated epilepsy

Generalized onset Tonic Clonic Seizures: Adults Recommendations

Level	AEDs
A	**None**
B	**None**
C	**CBZ*, PHT*, LTG, OXC, PB, PHT, TPM, VPA**
D	GBP, LEV, VGB
E	Others
F	None

*=may aggravate tonic clonic seizures and more commonly other generalized seizure types, should be used with caution

Optimal initial monotherapy for patients with newly diagnosed or untreated epilepsy

Juvenile Myoclonic Epilepsy: Adult Recommendations

Level	AEDs
A	**None**
B	**None**
C	**None**
D	TPM, VPA (ZNS, CZP, LTG*, LEV)
E	Others
F	CBZ*, GBP, OXC*, PHT*, TGB, VGB

*may aggravate myoclonic seizure types, should be used with caution

Table 4. Summary of studies and level of evidence for each seizure type and epilepsy syndrome

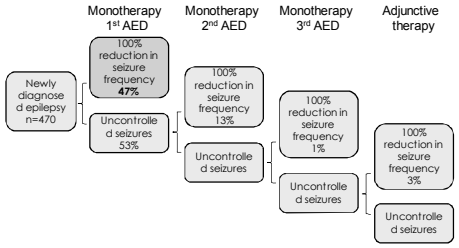
Seizure type or epilepsy syndrome	Class I studies	Class II studies	Class III studies	Level of efficacy and effectiveness evidence (in alphabetical order)
Adults with partial-onset seizures	4	1	34	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB Level D: CZP, PRM
Children with partial-onset seizures	1	0	19	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS
Elderly adults with partial-onset seizures	1	1	3	Level A: GBP, LTG Level B: None Level C: CBZ Level D: TPM, VPA
Adults with generalized onset tonic–clonic seizures	0	0	27	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB
Children with generalized-onset tonic–clonic seizures	0	0	14	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC
Children with absence seizures	1	0	7	Level A: ESM, VPA Level B: None Level C: LTG Level D: None
Benign epilepsy with centrotemporal spikes (BECTS)	0	0	3	Level A: None Level B: None Level C: CBZ, VPA Level D: GBP, LEV, OXC, STM
Juvenile myoclonic epilepsy (JME)	0	0	1	Level A: None Level B: None Level C: None Level D: TPM, VPA

Concepts of medical treatment

➨ Minimally effective dose → Maximally tolerated dose

- Sequential monotherapy
  - Ability of seizure control
  - Tolerability, toxicity, drug interaction
  - Compliance, cost
- Polytherapy (adjunctive treatment)
  - Same or "different" mechanisms of action
- Rational polytherapy
- Special considerations
  - Young, elderly, females conceptual age, pregnancy, specific medical conditions

Monotherapy



47% of the newly diagnosed epileptic patients achieved 100% reduction in seizure frequency with their first AED

Kwan P, Brodie MJ. Early identification of refractory epilepsy. NEJM 2000

The chance to be seizure free with

- 1st AED : 61.8%
- 2nd AED : 41.7%
- 5th AED : 16.6%
- 6th AED : 0%

Schiller Y, Neurology 2008

Administration

- Enteral: tablet, capsule, syrup
- Parenteral: IM, IV
- Other routes: buccal, intranasal, per-rectal
- Half-life, frequency of treatment
- Control released formulation
- Generic or original

Follow up plans

- Efficacy: seizure frequency (seizure diary)
- Side effects (tolerability)
- Quality of life
- Monitoring: blood level, EEG, CBC, Na, Cr, LFT

- Beware "phenomenon of regression to the mean"
  - Wide fluctuations in seizure frequency over time
    - Exacerbation-spontaneous amelioration

Prognostic groups

1) Spontaneous remission (20-30%)

- Benign epilepsy of childhood with centrotemporal spikes (BECT)
- Childhood absence epilepsy (CAE)

2) Remission on AEDs (20-30%)

- Most focal epilepsy
- Juvenile myoclonic epilepsy (JME)**

3) Persistent seizure with AEDs (30-40%)

- Refractory patients
  - An increase risk of psychosocial and medical morbidities and mortality

Kwan P, J Neurol Neurosurg Psych 2004, Schuele SU, Lancet Neurol 2008

Concerns

Precipitating factors

- Identify and avoid precipitating factors
  - Miss tablets (poor compliance)
  - Excessive sleep deprivation
  - Some photosensitive epilepsies
    - Intermittent flashing lights, certain video game
  - Excessive alcoholic drinking
  - Stress, fever, etc.

Precaution

- Driving
- Swimming
- Heights
- Some work environments
- Bath as opposed to shower

Summary

- The most important is to diagnose correctly
- Plans of initial management both pharmacological and non-pharmacological approaches are essential
- Evaluation and prompt treatments including using either standard or new AEDs should be done on a case-by-case basis
- Identify refractory epilepsy case and consider refer to Epilepsy centers at the proper time
- Some special conditions need to consider