TREATMENT OF FIRST SEIZURE IS CONTROVERSIAL:
- 16-62% of unprovoked sz will recur within 5 years
- Relapse rate may be reduced by antiepileptic drugs
  - > Relapse rate increased if:
    - Abnormal imaging
    - Abnormal neurological exam
    - Abnormal EEG
    - Family history
- Quality of life issues are important (i.e. driving)

TREATMENT RESISTANT EPILEPSY: 40-60% of epilepsy pts
- = failure of adequate trials of 2 tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combo) to achieve sustained sz freedom for at least 1 year
- "Drug resistant" replaces the terms medically intractable, refractory, pharmacoresistant

GOAL FOR THERAPY: maximize QOL by eliminating (or ↓ frequency) sz while minimizing ADEs
> NO neurodevelopmental or cognitive outcomes, comorbid mgment, psycho-social considerations

ANTIEPILEPTIC DRUG:
1) Decreases the frequency and/or severity of sz in people with epilepsy
2) Treats the sx of sz not the epileptic condition
3) Does not prevent the development of epilepsy (epileptogenesis) in individuals who have acquired a risk for seizures (ex// after head trauma, stroke, tumor)

VARIABLES THAT AFFECT INITIAL AED SELECTION

AED-specific variables	Patient-specific variables	Nation-specific variables
• Sz type or epilepsy syndrome specific efficacy or effectiveness • Dose-dependent AEs • Idiosyncratic rxns • Chronic toxicities • Teratogenicity • Carcinogenicity • Pharmacokinetics • Interaction potential • Formulations	• Genetic background • Age • Gender • Comedications • COMORBIDITIES • Insurance coverage • Ability to swallow pills/tablets	• AED availability • AED cost • Insurance coverage

AED PHARMACOLOGICAL STRATEGIES

1. Increase inhibitory transmission – **GABA (major inhibitory NT) receptors**

GABA-A RECEPTOR	GABA-B RECEPTOR
Ionotropic	Metabotropic
• Postsynaptic fast inhibition • Principally Cl- through pore	• Postsynaptic slow inhibition • Pre-synaptic reduction in Ca influx • Principally K+ channel activation

• Barbiturates and BZDs act on GABA-A directly to modify Cl- channel openings:
  o Barbiturates ↑ open duration
  o BZD ↑ open frequency
• Tiagabine inhibits GABA reuptake from synapses
• Vigabatrin elevates GABA levels by irreversibly inhibiting its main catabolic enzyme, GABA-transaminase
• Gabapentin was designed as a liphophilic GABA analogue, but does not function on the GABA receptor agonist	

- AEDs can:
  - Enhance GABA"s postsynaptic inhibition
  - Block GABA re-uptake into presynaptic terminals & glial cells
  - Block GABA transaminase (GABA-T) in terminals and glial cells

2. Decrease excitatory transmission – **GLUTAMATE (major excitatory NT) receptors**

Ionotropic: fast synaptic transmission	AMPA/Kainate	• Channels conduct primarily Na+	Topiramate: blocks AMPA receptor subtype on postsynaptic neuron reducing PDS
	NMDA	• Channels conduct both Na+ and Ca++ • Glycine is a neuromodulator	Felbamate: blocks glycine from binding, reducing NMDA channel activity
Metabotropic: slow synaptic transmission GPCR (2nd messengers) Modulate intrinsic & synaptic cellular activity	Group I mGluRs (mGluRs 1 and 5)	• Primarily postsynaptic/ perisynaptic • Net excitatory effect (ictogenic) • Couple to inositol triphosphate • Long-lasting effects (epileptogenic)	Direct glutamate receptor antagonists are effective against experimental seizures, but frequently cause psychosis and other neuropsychiatric adverse effects clinically
	Group II (mGluRs 2&3) and group III (4, 6, 7, 8)	• Primarily presynaptic • Net inhibitory effect (reduce NT release) • Negatively coupled to adenylate cyclase (reduce cAMP)	
• Phenobarbital: inhibits release of glutamate from presynaptic terminals • Lamotrigine: inhibits release of glutamate from presynaptic terminals			

3. Regulate cellular excitability by blocking ionic flux across membranes
- Mutant (dysfunctional) ion channels are principle genetic cause of epilepsy (can cause increase or decrease in function)
- **EXCITABILITY AND VOLTAGE GATED SODIUM CHANNELS:**
  - a) Na+ channels are activated (open) → Na+ ions rush in → cell depolarizes & spike activity begins
  - b) Na+ channels inactivate after opening, preventing current flow = refractory period (no AP can fire)
  - c) Recovery from inactivation resets Na+ channels to fire again
  - > Cyclical open → inactivate → recover → open cycle allows high-frequency spike burst in PDS (spread of abnormal synchronous discharge in network)
    - Sodium channels are blocked by a blocking particle (accessory sodium channel modulatory beta subunit) – NOT the inactivation gate
      - Blocking particle enters and blocks Na current → repolarization pushes the blocking particle out
      - Na current flows "resurgent current" and depolarizes the cell = premature & repeated AP generation → epilepsy & myotonia
        - Open → beta subunit block → still open
  - > Low-frequency Na+ firing is allowed with sodium-targeting AEDs
    - These drugs slow the rate of recovery from Na+ channel inactivation
    - Decrease high-frequency burst discharges but allow "normal" transmission
- **T-TYPE VOLTAGE GATED CALCIUM CHANNELS:**
  - Absence (3 Hz) spike wave seizures occur from reciprocal firing and stimulation in the thalamocortical network
    - Synchronous discharge of thalamic neurons that activate the cerebral cortex in waves occurring at 3/sec (3Hz) frequencies
    - This firing pattern is regulated and amplified by voltage-gated calcium channels with a lower voltage threshold (T) – aka T-type Cav3.x channels
  - AEDs: valproate, ethosuximide, zonisamide – reduce calcium current flow across the membrane to modulate TC firing

SUMMARY: MECHANISMS OF NEUROMODULATION

AED	Na+ channel blockage	Ca++ channel blockade	H-current enhancement	Glutamate receptor antagonism	GABA enhancement	Carbonic anhydrase inhibition	K+ channel enhancement
Phenytoin	X			X (NMDA glycine)			
CBZ, OXC, ESL	X				X (CBZ > OXC)		
Valproate	X	X			X		
Felbamate	X	X		X (NMDA)	X		
Lamotrigine	X		X	X (kainite)			
Topiramate	X	X		X (AMPA, kainite)	X	X	
Zonisamide	X	X				X	
Lacosamide	X (slow inact)						
Ruflinamide	X						
Barb, benzo					X (GABA-A)		
Ethosuximide		X					
Gabapentin		X	X	X (NMDA, glycine)			
Tiagabine					X (reuptake)		
Levetiracetam				X (kainite)			
Pregabalin		X					
Vigabatrin					X (metab)		
Ezogabine					X		X
Perrampanel				X (AMPA)			

DRUG INTERACTIONS

CAN OCCUR WHEN:
- Addition of a new medication when an inducer/inhibitor is present
- Addition of inducer/inhibitor to an existing medication regimen
- Removal of an inducer/inhibitor from chronic medication regimen

AEDS AND DRUG INTERACTIONS:

Induce metabolism of other drugs	Broad-spectrum inducers	• Carbamazepine • Phenytoin • Phenobarbital • Primidone
	Selective CYP3A (at higher doses) ; Selective CYP2C19	• Oxcarbazepine • Topiramate • Felbamate
DO NOT appear to be inducers or inhibitors of the CYP system include		• Gabapentin • Lamotrigine • Pregabalin • Tiagabine • Levetiracetam • Zonisamide • Lacosamide • Ezogabine • Perampanel

DISCONTINUING AED THERAPY:
- Requires seizure freedom for > 2 years
- Overall > 60% chance of successful withdrawal in some epilepsy syndrome

CONSIDERATIONS FOR WITHDRAWAL:
- Control achieved easily on one drug at low dose
- No previous unsuccessful attempts at withdrawal
- Normal neurologic exam and EEG
- Primary generalized seizures except JME
- Consider relative risks/benefits (ex// driving, pregnancy)

DISCONTINUING/MODIFYING THERAPY:
- Seizure recurrence after drug removed
- Change in seizure phenotype, severity, frequency

CONSIDERATIONS AND QUESTIONS:
- Is there an underlying progressive pathology?
  - Tumor, trauma, neurodegeneration
- Was there an (avoidable) provocation?
  - Infection, drug use
- If on AED:
  - Problem with compliance?
  - PK (drug metabolism) factor?
  - Increase dosage required?
  - Change AED or add on therapy?

AED ADVERSE EFFECTS:

Common adverse effects (typically dose-related)	Dizziness, fatigue, ataxia, diplopia	ALL AEDS
	Irritability, neuropsychiatric SEs	Levetiracetam, ezogabine
	Word-finding difficulty	Topiramate
	Weight loss/anorexia	Topiramate, zonisamide, felbamate
	Weight gain	Valproate, carbamazepine, gabapentin, pregabalin
Serious Adverse Events	Renal stones	Topiramate, zonisamide
	Anhydrosis, heat stroke	Topiramate, zonisamide
	Acute closed-angle glaucoma	Topiramate
	Hyponatremia	Carbamazepine, oxcarbazepine
	Urinary retention	Ezogabine
	Aplastic anemia	Felbamate, zonisamide, valproate, carbamazepine
	Heart failure	Valproate, felbamate, lamotrigine, phenobarbital
	Peripheral vision loss	Vigabatrin
	SJS / TEN (T-lymphocyte mediated)	Carbamazepine, ethosuximide, lamotrigine, phenobarbital, phenytoin > Rapid titration of lamotrigine especially in combo with valproate increases risk > HLA-B 1502 allele increasing SJS/TEN (almost exclusively Asians) for CBZ / OXC

LONG-TERM ADVERSE EFFECTS OF AEDS

Endocrine/ Metabolic Effects	Osteomalacia, osteoporosis (vit D deficiency or other)	Carbamazepine, barbiturates, phenytoin, oxcarbazepine, valproate
	Altered connective tissue metabolism or growth (facial coarsening, hirsutism, gingival hyperplasia or contractures)	Phenytoin, phenobarbital
	Polycystic ovarian syndrome	Valproic acid
Neurologic	Neuropathy	Phenytoin, carbamazepine
	Cerebellar degeneration	Phenytoin
Sexual Dysfunction		Phenytoin, carbamazepine, phenobarbital, primidone

PREGNANCY, EPILEPSY AND AEDS:

- 96% of pregnancies in mothers with epilepsy produce normal children
- There is an increased rate of fetal cranial malformations with antiepileptic drug exposure

Have significant risk of birth defects	Topiramate, phenobarbital, valproate
Teratogenic risk lower than valproate	Oxcarbazepine, zonisamide, gabapentin
Probably safest AEDs	Lamotrigine, levetiracetam, carbamazepine, phenytoin