CHOICE OF ANTIEPILEPTIC DRUGS:

1) Identify seizure type(generalized vs focal vs unknown)
2) Choosing an antiepileptic drug(AED)

GOALS

- Eliminate or reduce seizures
- Minimize side effects
- Maximize quality of life

IMPORTANT CONSIDERATIONS - know your AEDs and patient

- AED effectiveness for seizure type(s)
- Side effect profile – contributes to initial failure at approximately the same rate as efficacy
- Interactions - especially warfarin and oral contraceptives
- Medical history - especially hepatic or renal impairment and psychiatric history
- age, gender, and family planning
- lifestyle

- ~50% of patients with seizures are successfully treated with the first AED choice
- Failure usually results from breakthrough seizures vs intolerance of side effects
- Risk of failure is higher in patients of young age, female gender, GTC seizures, and with structural findings on imaging
- Monotherapy is preferred

SIDE EFFECTS – strategize

1) spread a medication over more doses if patient experiences peak level side effects
    - compare levels when patient is and is not experiencing side effects
    - patient use of a seizure calendar and journal may help to correlate symptoms with peak levels
    - ex. moving moving part of the AM dose to the PM dose might improve daytime sx
2) FDA warns that ALL AEDs increase suicidality; monitor for signs of worsening depression or suicidal ideation
3) Stevens-Johnson Sx(SJS), toxic epidermal necrolysis(TEN), and drug rash with eosinophilia and systemic symptoms(DRESS) are associated with carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, zonisamide, lamotrigine, and less commonly others

MAXIMIZE SUCCESS - start low and go slow

1) start with monotherapy
2) titrate to a dosage which is maximally tolerated and/or produces seizure freedom
3) monitor treatment at regular visits
4) drug levels can guide treatment
    - establish an individuals therapeutic range once control has been achieved
    - diagnosis of toxicity
    - assess adherence
    - guide dose adjustments with breakthrough seizures or suspected drug-drug interactions
5) educate the patient and family
    - importance of strict adherence
    - provide written instructions of AED regimen
    - advise consultation with prescriber or pharmacist before starting any new medications, OTCs, or supplements
    - encourage use of a seizure calendar and journal to document triggers and side effects

COMBINATION THERAPY – choosing smartly

1) different class
2) different side effect profile

- ~10-15% who fail monotherapy achieve seizure remission on combination therapy with two agents
- Each subsequent agent has a diminished chance of success
- Risk of failure is higher in patients with a history of status epilepticus, younger age at intractability, underlying mental retardation, longer duration of epilepsy, and symptomatic epilepsy
- ~80% of patients can become seizure free with treatment

Drug	MOA	Uses	Limitations	Advantages	Side Effects	Pearls
carbamazepine(CBZ) - oral	Na channel	FDA - epilepsy, complex partial, generalized tonic-clonic, mixed - partial and generalized convulsive seizures - secondarily generalized seizures	- ineffective for absence or myoclonic seizures - enzyme inducer; including autoinduction - reduce effectiveness of most OTCs	- extremely effective	- sedation, headache, dizziness, nausea, ataxia, rash, diplopia - aplastic anemia, agranulocytosis - LFT elevation - hyponatremia(SIADH) RARE - Stevens-Johnson HLA-B 1502 - serum sickness - pancreatitis - lupus sx - class D	- dose-related side effects at initiation = slow titration - Tx of trigeminal neuralgia, bipolar disorder, neuropathic pain - monitor CBC w/ diff, LFTs, Na, TSH, excess sedation
phenytoin(PHT) - oral - IV(requires cardiac monitoring) *fosphenytoin preferred	Na channel + Ca channel	FDA - complex partial seizures; generalized tonic-clonic seizures; Neurosurgery related seizures - partial and generalized convulsive seizures - secondarily generalized seizures - Lennox-Gastaut Sx - status epilepticus	- ineffective for absence or myoclonic seizures - enzyme inducer - highly protein bound = many drug-drug interactions - protein saturation may result in LARGE increases in serum levels - MANY side effects	- extremely effective	- gingival hypertrophy, rash, osteomalacia, folic acid deficiency - confusion, slurred speech, double vision, ataxia, nystagmus - RARE agranulocytosis, SJS/TEN, aplastic anemia, hepatic failure, serum sickness, adenopathy, pseudolymphoma, peripheral neuropathy, lupus sx, hirsutism - class D	- level corrected for albumin - supplement calcium and folic acid - monitor CBC + LFTs, trough concentrations - cardiac monitoring with IV formulation
oxcarbazepine(OCBZ) - oral	Na channel	FDA - partial seizures monotherapy and adjunct - see carbamazepine	- ineffective for absence or myoclonic seizures - NOT an enzyme inducer like CBZ - still reduces effectiveness of most OTCs	- markedly reduced side effect profile compared to CBZ	- sedation, headache, dizziness, nausea, ataxia, rash, diplopia - hyponatremia - RARE SJS/TEN, multiorgan sensitivity, agranulocytosis, pancytopenia, leukopenia - class C	- excellent for patients requiring polytherapy - monitor for si/sx hyponatremia(SIADH) vs serum Na during first 3 months - periodic CBC and TSH
lamotrigine(LTG) - oral	Na channel + glutamate	FDA - Epilepsy; adjunct for partial, generalized tonic-clonic seizures, & Lennox-Gastaut Sx FDA - monotherapy > 16yo - monotherapy for focal seizures, idiopathic generalized epilepsy, mixed seizure disorders, and absence seizures in children	- can worsen myoclonic seizures in children with JME or myoclonic epilepsy of infancy - inducing agents decrease levels - autoinducer at high levels	- no active metabolites - weak enzyme inducer	- few CNS side effects - rash in 5% on rapid titration - risk of Stevens-Johnson/TEN - lvl increases with VPA + risk of skin rxns - rare aseptic meningitis - class C	- SLOW TITRATION - preferred in elderly due to lack of CNS side effects - preferred agent during pregnancy - monitor LFTs
zonisamide(ZNS) - oral	Na channel + Ca channel	FDA - partial seizure adjunct - addn'l used as monotherapy - myoclonic epilepsy esp JME	- inducing agents decrease levels - requires hepatic and renal dosing	- broad spectrum can dose once daily - not an inducer	- somnolence, ataxia, anorexia, poor concentration, abnormal thinking, nervousness, fatigue, and dizziness - wt loss - RARE nephrolithiasis, SJS/TEN, aplastic anemia, agranulocytosis - metabolic acidosis - fevers and decreased sweating in children leading to hyperthermia - avoid with sulfa allergies - Class C	- monitor metabolic profile; bicarb level prior to starting
lacosamide(LAC) - oral - IV	Na Channel modulation + binds CRMP2	FDA - partial seizures adjunct - approved for monotherapy or adjunct tx of focal seizures	- may exacerbate Lennox-Gastaut Sx - may prolong PR interval; caution in heart block or with other agents that increase PR	- well tolerated - not an inducer - minimal protein binding - renal clearance	- dizziness, nausea, fatigue, vertigo, ataxia, diplopia - may prolongs PR interval - rare AV block, neutropenia, multiorgan sensitivity - Class C	- adjunct in refractory noncovulsive status epilepticus - monitor PR interval, AV block

Drug	MOA	Uses	Limitations	Advantages	Side Effects	Pearls
clobazam(CBZ) - oral	GABA-A	- not FDA approved - focal epilepsy	- TOLERANCE - efficacy has no clear correlation with plasma levels	- low anxiolytic & high sedative effects	- sedation, dizziness, ataxia, blurred vision, diplopia, irritability, aggression, depression, muscle fatigue, and weakness - salivation, nausea, constipation - rare resp depression, SJS/TEN - Class C	- prophylaxis for travel and stressful occasions - catamenial epilepsy
clonazepam(CLZ) - oral	GABA-A	FDA - monotherapy or adjunct for akinetic and myoclonic seizure; Lennox-Gastaut, absence - status epilepticus adjunct	-TOLERANCE - sedation - rarely exacerbates GTCs	- crosses BBB rapidly	- ataxia, hyperactivity, restlessness, irritability, depression, cardiovascular or respiratory depression - Class D	- withdrawal may induce status epilepticus - psychiatric withdrawal, insomnia, anxiety, psychosis, tremor - paradoxical hyperactivity in children - tx panic disorder - monitor CBC, LFTs, Cr periodically
phenobarbital(PHB) - oral - IM - IV	GABA-A + glutamate antagonism	FDA - not specified - generalized and partial seizures - status epilepticus	- powerful enzyme inducer - many drug-drug interactions - very long half-life - poorly tolerated due to side effects - less effective than PHT and CBZ for focal seizures	- cost effective; least expensive AED	- cognitive and behavioral alterations - hirsutism, osteomalacia, Dupuytren contractures - ataxia, nystagmus - skin hypersensitivity - porphyria - RARE agranulocytosis, SJS/TEN, hepatic failure, serum sickness, connective tissue contractures - Class B/D	- EtOH withdrawal - sedative - serum PHB, CBC, LFTs
primidone(PRM) - oral	GABA-A - metabolized to PHB + others	FDA - not specified - second line partial and generalized seizures	- intense side effects on initiation; decrease in 1wk - tolerance, dependence - enzyme inducer	- less sedating than phenobarbital in some patients	- nausea, rash, fatigue, lethargy, ataxia, depression, psychosis, decreased libido - macrocytic anemia - sleep disturbance - RARE agranulocytosis, SJS/TEN, hepatic failure, serum sickness, connective tissue contractures - Class N	- Tx essential tremor - primidone urine crystals in overdose - serum primidone and PHB levels; CBC baseline, 6mo, 12mo
tiagabine(TGB) - oral	GABA reuptake inhibitor	FDA - partial seizures adjunct - second line adjunct for partial or secondarily generalized seizures	- adjunct use only - caution in patients with Hx of status epilepticus	- no significant interactions - side effects uncommon - not associated with end-organ toxicity	- abdominal pain - dizziness, nausea, asthenia, nervousness, tremor, depressed mood, emotional lability, poor concentration - diarrhea RARE SJS/TEN, non-convulsive status epilepticus - Class C	- might provoke seizures or status when used without concurrent first line therapy in patients with generalized epilepsy - monitor periodic LFTs
vigabatrin(VGB) - oral	GABA-T inhibitor	FDA - adjunct for refractory complex partial seizures FDA - nfantile spasms esp in tuberous sclerosis - monotherapy for refractory complex partial seizures	- requires SHARE registration - enzyme inducer - may worsen myoclonic seizures or generalized absence seizures	- renal excretion	- drowsiness, fatigue, headache, dizziness, depression, wt gain - RARE hypersensitivity and angioedema, MRI abnormalities - Class C	- BLACK BOX permanent visual field constriction; field testing required at initiation and every 6mo - DWI abnormalities on MRI

Drug	MOA	Uses	Limitations	Advantages	Side Effects	Pearls
ethosuxamide(ETX) - oral	T-type Ca channels	FDA - absence seizures(petit mal)	- NO activity against GTCs or focal seizurs	- favorable side effect profile compared to valproic acid	- nausea, vomiting - sleep disturbance - psychotic episodes - rare agranulocytosis, aplastic anemia, SJS/TEN, hepatic failure, serum sickness, dermatitis - Class N	- ABSENCE ONLY - monitor CBC, plts, LFTs, urinalysis
felbamate(FBM) - oral	blocks NMDA glutamate receptors + enhances GABA	- restricted to severe partial epilepsy or Lennox-Gastaut - highly refractory seizures *not a first-line treatment	- fatal toxic effects - not well tolerated - enzyme inducer and inhibitor - polytherapy increases adverse effects	- very effective - possible neuroprotection	- insomnia, anorexia, nausea, headache, irritability - wt loss - rare plastic anemia, hepatic failure - Class C	- CAUTION - aplastic anemia & hepatic failure - baseline LFTs, CBC w dif; monitor frequently
topiramate(TPM) - oral	blocks NMDA glutamate receptors & Na channels + enhances GABA	FDA - initial monotherapy for partial-onset or primary generalized tonic-clonic seizures FDA - adjunct for partial-onset, primary generalized tonitc-clonic, or Lennox-Gastaut -adjunct for refractory status epilepticus	- enzyme inducer and inhibitor - poor adherence due to cognitive effects	- very effective	- paresthesias, headache, fatigue, dizziness, depression, anxiety, mood problems, somnolence, difficulty concentrating, confusion, tremor - wt loss - nephrolithiasis - decreased sweating -> hyperthermia* *mostly in children - RARE acute myopia and glaucoma - Class D	- prophylaxis for migraines - tx EtOH dependence - appetite suppression; wt loss - frequent metabolic acidosis - CNS carbonic anhydrase inhibitor-> tx IIH - cognitive slowing and speech difficulty - baseline CO2 + Cr
perampanel(PER) - oral	glutamate antagonist (AMPA)	FDA - partial seizure adjunct - adjunct focal onset and primary generalized tonic clonic	- prolonged and variable half-life - not recommended in hepatic impairment - induced by inducers		- dizziness, somnolence, headache, fatigue, irritability, aggression, gait disturbance, falls - wt gain - Class C	BLACK BOX - mood and aggression - schedule III
valproate(VPA) - oral - IV	MANY - enhances GABA - glutamate inhibition - Na & T-type Ca channel modulation	FDA - complex partial and absence mono or adjunct therapy - idiopathic generalized epilepsy - juvenile myoclonic epilepsy - myoclonus - Lennox Gastaut - infantile spasms	- side effects - highly protein bound - enzyme inhibitor - displaces diazepam	- broad spectrum	- nausea, vomiting, dizziness, tremor - wt gain, allopecia, easy bruising - initial ALT elevation in 5-10% - RARE agranulocytosis, TSH elevation, PCOS, hepatic failure pancreatitis, SJS/TEN, serum sickness - rare reversible parkinsonism - Class X(migraine)/D(all others)	- TERATOGENICITY - neurodevelopmental abnormalities; FOLIC ACID - hyperammonemia encephalopathy tx carnitine - Tx migraine headache, bipolar disorder - baseline LFTs, CBC, plts; frequent monitoring required
gabapentin(GBP) - oral	alpha2delta Ca channel seems to enhance GABA synthesis	FDA - partial seizures adjunct - monotherapy for focal epilepsy	- antacids reduce bioavailability	- no drug interactions - not metabolized - no protein binding - no enzyme induction - renal excretion	- drowsiness, dizziness, ataxia, fatigue; effects are MILD - rare multiorgan hypersensitivity - Class C	- Tx neuropathic pain, RLS, postherpetic neuralgia, diabetic neuropathy, postoperative pain, hot flashes
pregabalin(PGB) - oral	alpha2delta Ca channel + addn'l NT modulation	FDA - partial seizures adjunct	- may worsen myoclonic epilepsy	- no drug interactions - not metabolized - no protein binding - no enzyme induction - renal excretion	- dizziness, somnolence, ataxia, tremor, peripheral edema, dry mouth - wt gain - rare angioedema, hypersensitivity rxns, rhabdomyolysis, myoclonus - Class C	- Tx diabetic neuropathy, postherpetic neuralgia, fibromyalgia - may cause euforia; schedule V
levetiracetam(LEV) - oral - IV	partly unknown binds SV2A protein modulates GABA	FDA - adjunct for partial, myoclonic(JME), and generalized tonic-clonic - broad spectrum - often used as monotherapy for focal seizures		- broad spectrum - effective in very young children - no enzyme induction - no significant interactions - no titration needed	- fatigue, somnolence, dizziness - agitation, anxiety, irritability, aggression, depression - URIs - rare SJS/TEN, pancytopenia, psychosis - Class C	- caution in mood disorders