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NEUROLOGY CASE STUDIES IN PRIMARY CARE

OBJECTIVES

1. Recognize differential diagnosis for symptoms of presenting neurologic disorders in primary care
2. Determine appropriate interventions/assessment to narrow down the differential list.
3. Develop an appropriate treatment plan, including pharmacologic interventions. .

DISCLOSURE

SPEAKER HAS NO RELATIONSHIPS OR FINANCIAL INTERESTS TO DISCLOSE

CASE STUDY #1

37-year-old
Female

CC: Tremor

Differentials:

1. Electrolyte disturbances
2. Resting tremor
3. Parkinsonian Tremor
4. Multiple Sclerosis
5. Active "Essential" tremor
6. Substance Abuse/Withdrawal
7. Chorea
8. CVA
9. Brain tumor
10. Spinal lesion

CASE STUDY #1: 37-YEAR-OLD, TREMOR

HISTORY

- Substance Abuse (Clean for 2 years)
- Tobacco use: 20 pack year
- No daily medications
- G3P3A1L2
- Hx of Migraines
- Hx of Hashimoto Hypothyroidism
- Surgery: ORIF of right ankle 15 years ago; Cholecystectomy 4 years ago
- Mom: Breast Cancer, Diabetes
- Dad: Hypertension, MI

CASE STUDY #1: 37-YEAR-OLD, TREMOR

History of Present Illness

- Complains of eye twitching
- Oral, chewing type movements have been reported by family members, but patient doesn't notice them
- Rhythmic tapping of the fingers on the right hand
- Symptoms come and go and are sometimes worse than other times
- Hx of reflux, out of medications
- History of migraines with aura: 2 in the past month

CASE STUDY #1:

37-YEAR-OLD, TREMOR

What does your exam look like?

- mental status
- cranial nerves
- motor system
- reflexes
- sensory system
- coordination
- station and gait

Consider these differentials?

1. Electrolyte disturbances
2. Resting tremor
3. Parkinsonian Tremor
4. Multiple Sclerosis
5. Active "Essential" tremor
6. Substance Abuse/Withdrawal
7. Chorea
8. CVA
9. Brain tumor
10. Spinal lesion

CASE STUDY #1:

37-YEAR OLD, TREMOR

SUBJECTIVE FINDINGS

- Blood pressure: 120/76
- Pulse 102, Regular
- Temp: 97.9 deg F
- Height: 5'2"
- Weight: 135 lbs
- BMI: 25
- Pulse ox: 98%

Number	Name of Nerve	Function	Assessment
CN I	Olfactory	Smell	Not Tested
CN II	Optic	Vision	Visual Acuity 20/30 corrected; No papilledema
CN III	Oculomotor	Eye Movement, Pupillary constriction	PERRLA; No nystagmus
CN IV	Trochlear	Eye Movement	Normal
CN V	Trigeminal	Facial sensation & Movement	Normal
CN VI	Abducens	Eve Movement	Normal

Number	Name of Nerve	Function	Assessment
CN I	Olfactory	Smell	Not Tested
CN VII	Facial	Corneal sensation & Facial Movement/Expression	Normal
CN VIII	Acoustic	Hearing	Normal via whisper test
CN IX	Glossophary ngeal	Taste; swallowing; uvula; soft palate	Normal – Taste deferred
CN X	Vagus	Taste; swallowing; uvula; soft palate	Normal – Taste deferred
CN XI	Spinal Accessory	Neck & shoulder strength/movement	Normal
CN XII	Hypoglossal	Tongue Movement	Normal w/movement, fasciculations at rest

CASE STUDY #1: 37-YEAR-OLD, TREMOR

- Negative Romberg
- 5/5 Strength in all extremities
- Intact sensation
- No pronator drift
- Normal gait
- No rigidity with movements

Notes on Observation:

- "Piano playing" movement of fingers on the right hand at rest
- Facial movements around the mouth area
- No visual eye twitching

DIFFERENTIAL WORK-UP

Case Study #2: 37-Year-Old, Tremor

- **Reflexes, Motor, Reflexes, Balance, Gait:** Normal
- **Electrolytes:** Normal
- **ALT/AST:** Elevated slightly
- **Urine Drug Screen:** Negative
- **ANA:** Negative
- **ESR, CRP:** Negative
- **CBC:** WNL
- **CT Brain:** Negative

ANY CHANGE IN DIFFERENTIALS?

Case Study #2: 37-Year-Old, Tremor

- ~~Electrolyte disturbances~~
- Resting tremor
- Parkinsonian Tremor
- ~~Multiple Sclerosis~~
- Essential tremor
- ~~Substance Abuse/Withdrawal~~
- Chorea process
- ~~CVA~~
- ~~Brain tumor~~
- ~~Spinal lesion~~

CASE STUDY #1: DIFFERENTIALS REMAINING

- ~~Chorea Process~~
- Resting tremor
- Parkinsonian Tremor
- ~~Essential tremor~~

AIMS (Abnormal Involuntary Movement Scale)

0 = NONE
1 = MINIMAL
2 = MILD
3 = MODERATE
4 = SEVERE

- **Facial & Oral Movements:**
  - Muscles of Facial Expression (e.g. movements of forehead, eyebrows, periorbital area, cheeks, grimacing, etc.)
  - Lips and Periorbital Area (e.g. puckering, pouting, smacking)
  - Jaw (e.g. biting, clenching, chewing)
  - Tongue (rate increases in movement in and out of mouth. Not inability to sustain movement. Darting in and out of mouth).
- **Dental Status**
  - Current problems with teeth/dentures? **NO**
  - Are dentures usually worn? **NO**
  - Edentia? **NO**
  - Do movements disappear in sleep? **YES**

AIMS (Abnormal Involuntary Movement Scale)

RATING OF ≥2
OR
2 AREAS W/MILD TD
OR
1 AREA W/MODERATE MOVEMENTS

Extremity Movements

- **Upper Extremities:** Include choreic movements, athetoid movements. DO NOT INCLUDE TREMOR (i.e., repetitive, regular, rhythmic)
- **Lower Extremities: (**e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot)

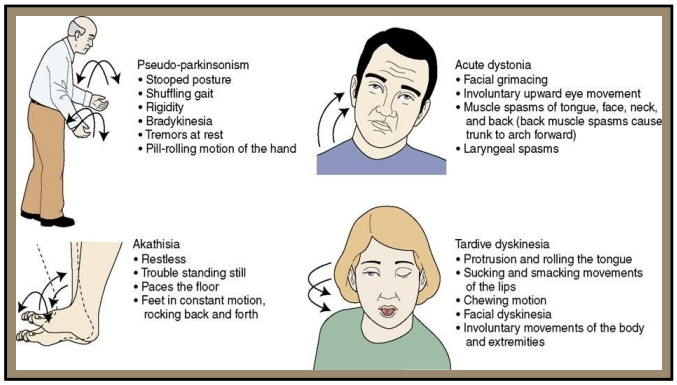
Trunk Movements

- **Neck, shoulders, hips (**e.g., rocking, twisting, squirming, pelvic gyrations)

Global judgements

- Severity of abnormal movements overall
- Incapacitation due to abnormal movements
- Patient's awareness of abnormal movements (0-4)

Do movements disappear in sleep?



DX: TARDIVE DYSKINESIA? OR DI PARKINSONISM

HX SAID NO MEDICATIONS?

CASE STUDY #1

MEDICATION LIST

- Levothyroxine (Synthroid) 125 mcg po daily
- Pantoprazole (Protonix) 20mg po daily
- Topiramate (Topamax) 100 mg po BID
- Sumatriptan 50mg po as needed for migraine (max 200mg/24 hour)
- Lithium 400mg in the AM and 600mg in the PM

Medications Associated With Tardive Syndromes
(Dopamine Receptor Blocking Agents)

- Haloperidol (Haldol)
- Droperidol (Inapsine)
- Chlorpromazine (Thorazine)
- Prochlorperazine (Compazine)
- Risperidone (Risperdal)
- Quetiapine (Seroquel)
- Paliperidone (Invega)
- Olanzapine (Zyprexa)
- Aripiprazole (Abilify)
- Metoclopramide (Reglan)
- Doxepin (Silenor)
- Amitriptyline (Elavil)

SSRIs (i.e. fluoxetine (Prozac)) or SNRIs (i.e. duloxetine (Cymbalta)) not likely to cause TD, but may cause akathisia

SUSPECTED DIAGNOSIS?

HOW DO YOU DIFFERENTIATE BETWEEN TD AND DI PARKINSONISM?

TARDIVE DYSKINESIA	CHARACTERISTICS	DRUG-INDUCED PARKINSONISM
>3 MONTHS	**ONSET**	HOURS-WEEKS 90% WITHIN 3 MONTHS
ABNORMAL FACIAL MOVEMENTS (LIP SMACKING, PUCKERING, CHEWING, OR TONGUE PROTRUSION)	**SYMPTOMS**	RESTING TREMOR, BRADYKINESIA, RIGIDITY
DEPENDS ON DETECTION	**REVERSIBILITY**	YES, BUT MAY TAKE UP TO A YEAR
DECREASE DOPAMINE ACTIVITY	**TREATMENT**	INCREASE DOPAMINE ACTIVITY

TARDIVE DYSKINESIA

Schooler and Kane criteria:

1) The use of antipsychotic drugs for at least three months
2) Involuntary movements of moderate intensity observed at least in one region or of mild intensity in at least two regions,
3) Exclusion of other conditions that cause movement disorders

TARDIVE DYSKINESIA

The DSM-V defines tardive dyskinesia as a medication-induced movement disorder that persists despite discontinuation or change of the medications, persisting at least 4 weeks after discontinuation.

- **Movements worsen with:**
  - Emotional stress
  - Diminish with sedation
  - Remit during sleep
- **Very common to first appear:**
  - After a reduction in drug dose
  - After switching to a less potent dose
  - Following discontinuation of an offending drug

TARDIVE DYSKINESIA

- More prevalent in women
  - Especially postmenopausal
- ~20-30% of general population w/antipsychotic use
- ~40-47% in the elderly
- Increased with:
  - Anticholinergics + Neuroleptics
  - Dopamine Antagonists (1st generation)
  - Comorbidities (i.e. diabetes)
  - Younger age of exposure
  - Presence of extrapyramidal symptoms early in treatment.

CASE STUDY #1: *TARDIVE DYSKINESIA*

TREATMENT/ FOLLOW UP

- PREVENTION
- RECOGNIZE
- REMOVAL OF THE OFFENDING AGENT
- PROGNOSIS
- PHARMACOLOGIC TREATMENT

REMOVAL OF OFFENDING AGENT?

Is ongoing treatment necessary?

YES

- Consult with Psych/Neuro
- Continue DRBA
  - If on a 1st generation DRBA
    - Switch to a 2nd generation DRBA
  - If on a 2nd generation DRBA
    - Decrease to lowest effective dose
    - Switch to lower risk drug

NO

- Consult with Psych/Neuro
- Discontinue DRBA
  - Taper gradually
  - TD may worsen during taper
  - May take months to improve or never
  - Avoid DRBA's in the future!

Persistent moderate to severe TD
Focal dystonia (e.g. cervical, blepharospasm)

PERSISTENT, MODERATE TO SEVERE TD

First-Line

- **Tetrabenazine (Xenazine)**
- **Velbenazine (Ingrezza)**
- **Deutetrabenazine (Austedo)**

Second line (Mild symptoms)

- Benzodiazepines

Tardive dystonia

- Botulinum toxin injection

Persistent despite symptomatic therapies

- Refer to movement disorder specialist

ZIWMGYPEV$Q SRSEQ MRI$ XVERWTSVXIV16 MRLMFMKSVW

- MOA: Depletes dopamine storage in presynaptic vesicles
  - Suppresses TD movements
- Tetrabenazine – released in 2008; dosing TID
- Released in 2017
  - Valbenazine: Daily dosing (QD)
  - Deutetrabenazine: Twice daily dosing (BID)
  - Newer agents have longer half-life
  - No head-to-head studies
  - All show benefit over placebo

- Side Effects
- Common: Somnolence and fatigue
- Less Common:
  - Akathisia
  - Parkinsonism
  - Depression
  - Tremor
  - Insomnia
  - Confusion
- Black Box: Depression and suicidality

CLINICAL VIGNETTE

54-year old male

Dx: CHF, COPD, Diabetes, Type 2, Diabetic Gastroparesis

ON: Reglan + many other oral medications for chronic conditions

HOW DO YOU DIFFERENTIATE BETWEEN TD AND DI PARKINSONISM?

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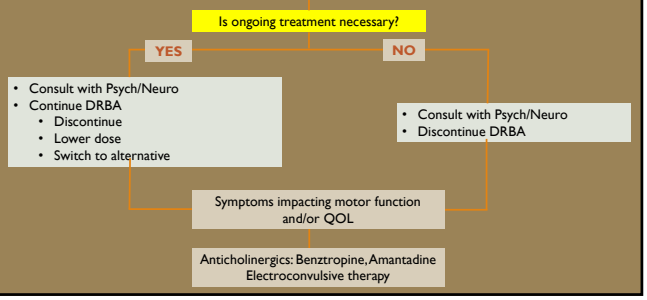
DECREASE DOPAMINE ACTIVITY	**TREATMENT**	INCREASE DOPAMINE ACTIVITY

Medications Associated With DI Parkinsonism
(Dopamine Receptor Blocking Agents)

Haloperidol (Haldol)	Quetiapine (Seroquel)
Droperidol (Inapsine)	Hydroxyzine
Chlorpromazine (Thorazine)	Promethazine (Phenergan)
Lithium (Lithobid)	Metoclopramide (Reglan)
Prochlorperazine (Compazine)	Doxepin (Silenor)
Risperidone (Risperdal)	Amitriptyline (Elavil)

SSRIs (i.e. fluoxetine (Prozac)) or SNRIs (i.e. duloxetine (Cymbalta))

REMOVAL OF OFFENDING AGENT?



ACTION "ESSENTIAL" TREMOR

Evaluate for Secondary Causes	
Conditions	Hyperthyroidism Hypo or Hypercalcemia
Medications	Antiarrhythmic drugs Antidepressants (SSRIs, SNRIs, TCAs) Antiseizure medications Beta agonists Glucocorticoids Stimulants Lithium Caffeine Nicotine Alcohol withdrawal

CORE Criteria for Diagnosis

- Bilateral upper extremity action tremor
- Absence of other neurologic signs
- With or without head, voice, and/or lower limb tremor

Secondary Criteria

- Long duration (>3 years)
- Positive family history
- Beneficial response to alcohol

TREATMENT

DISABLING ESSENTIAL TREMOR

PROPRANOL
60-80 MG/DAY BID-QID

OR/AND

PRIMIDONE
25-250 MG/DAY QHS
MAX 750 MG/DAY

- EFFICACY: REDUCE TREMOR BY 50%
- DURATION: ONE YEAR

CASE STUDY #2
22-YEAR-OLD MALE F/U ER VISIT FOR NEW ONSET SEIZURE

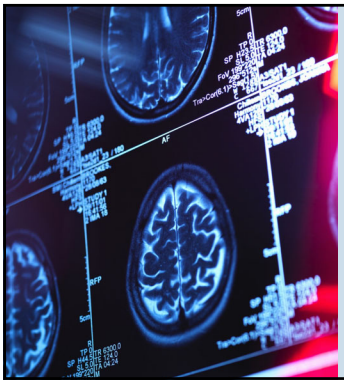
DIFFERENTIAL DIAGNOSIS

Syncope
Transient ischemic attack (older adults; ASCVD risk)
Migraine
Panic attack and anxiety
Psychogenic nonepileptic seizure
Transient global amnesia (rare before the age of 50 years)
Narcolepsy with cataplexy
Paroxysmal movement disorders

CASE STUDY #2: HPI

22-YEAR-OLD NEW ONSET SEIZURE

- Seizure described as staring with rhythmic tapping of the fingers and mouth movements.
- Lasted for approximately 2 minutes, witnessed by wife
- No memory of events
- Had a headache for several hours after
- Discharged from ER to f/u with Primary Care
  - No Medications Ordered



CASE STUDY #2: NEW ONSET SEIZURE

Differentials:

1. Provoked
2. Unprovoked

CASE STUDY #2

IS IT A PROVOKED (ACUTE INSULT) SEIZURE?

25-30% of first seizures

Differentials:

- Metabolic derangements
- Drug or alcohol withdrawal
- Acute neurologic disorders
  - Stroke
  - Encephalitis
  - Acute head injury

DIFFERENTIAL WORK-UP ER RECORDS REVIEW

*FEMALE:
ADD PREGNANCY TEST

- **ELECTROLYTES: NORMAL**
- **GLUCOSE: NORMAL**
- **LIVER FUNCTION: NORMAL**
- **RENAL FUNCTION: NORMAL**
- **URINE DRUG SCREEN: NEGATIVE**
- **CBC: NORMAL**
- **URINALYSIS: NORMAL**
- **CT BRAIN: NEGATIVE**
- **ECG: NORMAL**
- **SERUM LACTATE: ELEVATED**

MEDICAL HISTORY

CASE STUDY #2: NEW ONSET SEIZURES

TRIGGERS: Reports working nights and not getting much sleep

- Strong emotions; Intense exercise; Loud music; Flashing lights
- Fever
- Females: Menses, Pregnancy

PRIOR SEIZURE EVENTS

- Not to his knowledge

FAMILY HX OF SEIZURES

- 1st cousin with seizures. Not sure of type

MEDICAL HISTORY TRIGGERS

CASE STUDY #2: NOT SIGNIFICANT

- Head injury
- Abnormal early neurologic development or intellectual disability
- Stroke
- Alzheimer disease
- History of intracranial infection
- Alcohol or drug abuse
- History of cancer
- Rheumatologic disorders such as systemic lupus erythematosus
- Hematologic disorders including sickle cell disease, porphyria, and antiphospholipid syndrome

MEDICATION TRIGGERS

CASE STUDY #2: NOT SIGNIFICANT

OTC Medications:

- Analgesic Opioids: Tramadol
- Anticancer: Methotrexate

Antimicrobials: Carbapenems (eg, imipenem); Cephalosporins (fourth generation); Fluoroquinolones (eg, ciprofloxacin)

Immunosuppressants: Cyclosporine

Psychiatric Medications: Antipsychotics, Bupropion, Buspirone, Lithium, SSRIs, SNRIs, TCAs

Stimulants: Amphetamines, Methylphenidate

Sympathomimetics and decongestants: Anorexiants (nonprescription diet aids); Phenylephrine; Pseudoephedrine

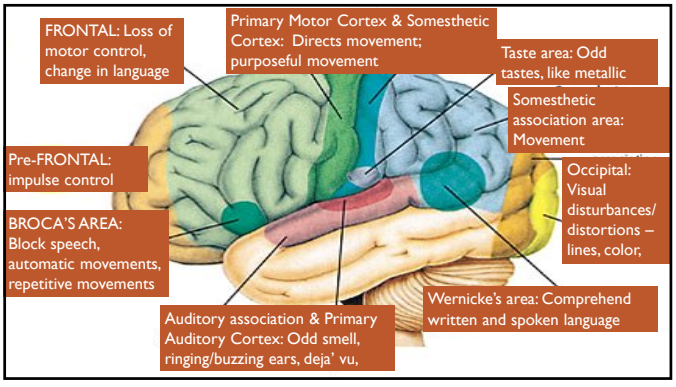
CASE STUDY #2 UNPROVOKED SEIZURES

- Idiopathic
- Preexisting lesion
- Progressive nervous system disorder
  - Amyotrophic Lateral Sclerosis (ALS)
  - Parkinson's Disease
  - Alzheimer's Disease
  - Huntington's Disease

Type of Seizure	Other names	Characteristics
Focal Seizures w/retained awareness	Simple Partial Seizures	Occurs in a focal area of the brain Symptoms depend on area involved <2 minutes Fully alert, able to interact/Frozen
Focal Seizures impaired awareness	Complex Partial Seizures, Temporal Seizures, Psychomotor Seizures	Focal areas of the brain Temporal & Frontal Automatisms: Involuntary movements Decrease or Absence of Awareness 30 sec to 3 minutes Post-ictal phase
Generalized Seizures	Grand Mal, major motor seizures, convulsions	Abrupt loss of consciousness All muscles become stiff (Tonic) Followed by rhythmic jerking (Clonic) 1-3 minutes Loss of Bowel/Bladder Post-ictal phase

GENERALIZED SEIZURES SUBTYPES

- Absence (Petit Mal)
- Clonic
- Tonic
- Myoclonic
- Atonic (Drop Seizures)



CASE STUDY #2: 22-YEAR-OLD, NEW ONSET SEIZURE

- CN II-XII Grossly Intact
- Negative Romberg
- 5/5 Strength in all extremities
- Intact sensation
- No pronator drift
- Normal gait
- No rigidity with movements
- No abnormal movements

PHYSICAL EXAM

NO SEIZURE RELATED TRAUMA

FURTHER DIFFERENTIAL WORK-UP

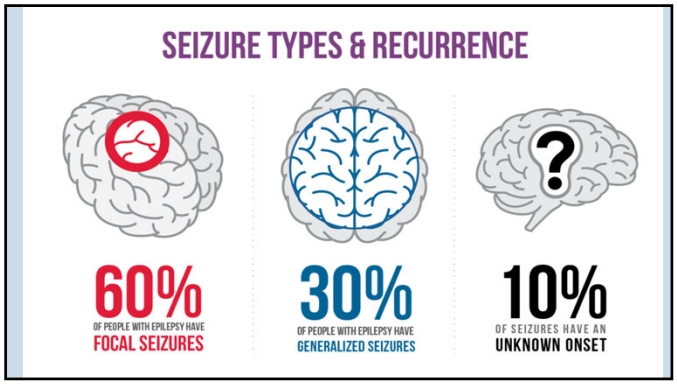
ANA

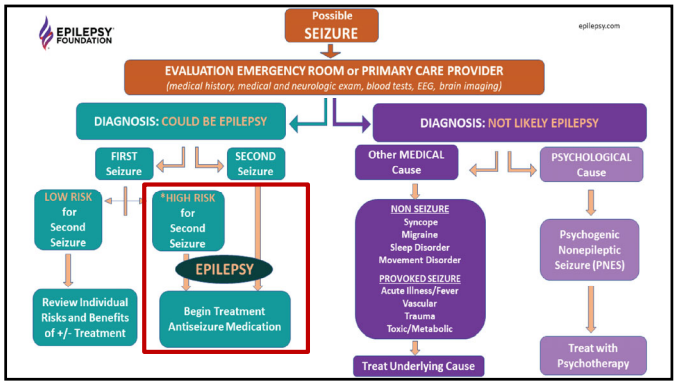
EEG: 25% will be abnormal

- Normal EEG does not rule out epilepsy

MRI: >50% will be normal

- Young-middle age
  - Mesial temporal sclerosis (Scarring deep temporal lobe)
  - **Sequelae of head injury**
  - **Congenital anomalies**
  - Brain tumors
  - Cysticercosis (tapeworm)
  - Vascular lesion (AV malformation)





RISK FOR RECURRENCE UNPROVOKED

40-50% of patients will have recurrent seizure within 2 years

Risks increase:

- **Abnormal EEG**
- **Remote symptomatic cause**, identified by clinical history or neuroimaging (eg, brain tumor, brain malformation, prior central nervous system infection)
- **Abnormal neurologic examination**, including focal findings and intellectual disability
- A **first seizure that occurs during sleep**

CASE STUDY #2

22-YEAR-OLD MALE

NEW ONSET FOCAL IMPAIRED AWARENESS

EEG: Normal

MRI: Normal

Works nights, little sleep

PROVOKED? UNPROVOKED?

EPILEPSY

- 2 or more unprovoked seizures occurring 24 hours apart
- One unprovoked seizure and a probability of future seizures
  - Recurrence risk >60%
  - Stroke
  - Central nervous system infection
  - TBI
- Diagnosis of an epilepsy syndrome

CASE STUDY #2: 22-YEAR-OLD

UNPROVOKED SEIZURE

Shared decision making

- **35% risk of recurrence**
- **Little impact on long-term outcomes**
- **Weigh risk of recurrence with side effects of medication**

TREATMENT?

Reasonably deferred until second seizure

MANAGING EPILEPSY

Main Goals

- Control seizures
- Avoid treatment side effects
- Maintain or restor quality of life

Choosing a Drug

- Drug Effectiveness
- Side effect profile
- Drug-drug interactions
- Age and Gender
- Lifestyle & patient preference
- Cost

Broad Spectrum Focal/Generalized	Narrow Spectrum Focal	Narrow Spectrum Absence
Valproate (Depakote)	Carbamazepine (Tegretol)	Ethosuximide (Zarontin)
Lamotrigine (Lamictal)	Gabapentin (Neurontin)	
Topiramate (Topamax)	Oxcarbazepine (Trileptal)	
Felbamate (Felbatol)	Phenobarbital	
Levetriacetam (Keppra)	Phenytoin (Dilantin)	
Zonisamide (Zonegran)	Pregabalin (Lyrica)	
Brivaracetam (Briviact)	Primidone (Mysoline)	
Clobazam (Sympazan)	Lacosamide (Vimpat)	
Perampanel (Fycompa)	Tiagabine (Gabitril)	
Rufinamide (Banzel)	Vigabatrin (Vigadrone)	
	Cenobamate (Xcopri)	
	Eslicarbazepine (Aptiom)	
	Stiripentol (Diacomit)	

Drug	Systemic Side Effects	Neurologic Side Effects
Carbamazepine (Tegretol)	Nausea, vomiting, diarrhea, hyponatremia, rash, pruritus	Drowsiness, dizziness, blurred or double vision, lethargy, headache
Oxcarbazepine (Trileptal)	Monitor levels closely during pregnancy	Similar to carbamazepine (Tegretol)
Zonisamide (Zonegran)	Nausea, anorexia	Somnolence, dizziness, ataxia, confusion, difficulty concentrating, depression
Lamotrigine (Lamictal)	Rash, nausea	Dizziness, tremor, diplopia
Oxcarbazepine (Trileptal)	Nausea, rash, hyponatremia	Sedation, headache, dizziness, vertigo, ataxia, diplopia
Pregabalin (Lyrica)	Weight gain, peripheral edema, dry mouth	Dizziness, somnolence, ataxia, tremor

GENERAL PATIENT SCENARIOS

Scenario	Recommended treatment
Initial treatment of focal epilepsy	Lamotrigine, Levetiracetam, Oxcarbazapine, Carbamazepine, Lacosamide
Childbearing female with genetic generalized or focal epilepsy	Lamotrigine, Levetiracetam
Older adult with focal epilepsy	Lamotrigine, Levetiracetam, Lacosamide
Hepatic Failure	Levetiracetam, Gabapentin, Lacosamide
Renal failure on hemodialysis	Lamotrigine, Oxcarbazepine, Levetiracetam

LEVETIRACETAM (KEPPRA)

- Frequently used for seizures
- Broad-spectrum
- Not metabolized in the liver
- Does not bind to blood proteins
- Common side effects:
  - Dizziness
  - Fatigue
  - Insomnia
  - Irritability
  - Mood changes
  - Infection
- Low incidence of causing thinking/memory problems

SEIZURE MANAGEMENT IN PRIMARY CARE

Family Planning/Pregnancy Assessment

- Avoid Sodium Valproate (Depakote) in child-bearing years

Osteoporosis

Emergency management of seizures in the community

- Buccal midazolam
- Rectal diazepam

MONITORING

- Missed doses
- Educate about side effects
- Adherence to treatment
- AED serum monitoring
  - Not routinely recommended
- Indications for monitoring of AED levels are:
  - Detection of non-adherence
  - Suspected toxicity
  - Adjustment of dosing
  - Management of pharmacokinetic interactions
  - Specific clinical conditions

PHENYTOIN (DILANTIN)

- Inexpensive
- Common side effects: unsteadiness and moderate cognitive problems.
- **Long term:** Hirsutism, Gingival hyperplasia, Enlarged facial features, Osteoporosis
- **Therapeutic window**:
  - The target serum level is 10-20 mcg per ml.
- Drug-Drug interactions
- Avoid alcohol

PATIENT EDUCATION

- Education about triggers
- Avoid unsupervised activities (i.e. swimming)
  - Personal injury, accidental death, suicide
- Driving
  - States vary in requirements
  - Most require some abstinence
  - Reporting responsibilities

REFER TO NEUROLOGY

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QUESTIONS?