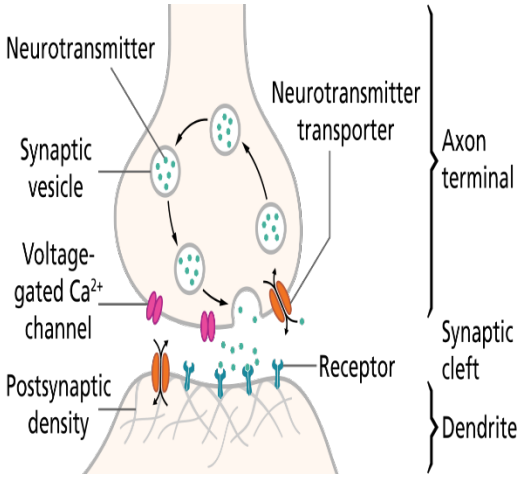
GUIDED LECTURE NOTES
ADVANCED PHARMACOTHERAPUTICS
CENTRAL NERVOUS SYSTEM

LEARNING OUTCOMES

1. Review Pathophysiology
2. Clinical Pharmacology
3. Mechanism of action
4. PK/PD
5. Medication/Interactions
6. ADR's -Adverse drug reactions
7. RBA (Risk Benefit Analysis/Stratification)



Medications to include

- Stimulants
- Anticonvulsants

A&P REVIEW

- CNS
  - Consists of the brain, spinal cord; Contains most of the nervous system
  - Coordinates the activity of all parts of the body
- The brain and spinal cord serve as the main "processing center" for the entire nervous system and control all the workings of the body.
- Millions of neurons provide the capacity to reason, experience feelings, and understand the world.
- Neurons provide the capacity to remember numerous pieces of information.

Neurotransmitters (know whether excitatory or inhibitory)

Neurotransmitter	Action and effects
Acetylcholine	
GABA(gamma-aminobutyric acid)	
Glutamate	
Glycine	
Dopamine	
Norepinephrine	
Serotonin	

ANOREXIANTS

- Medications include:
  - Diethylpropion
    - Tenuate, Tenuate Dospan (Category IV)
  - Phendimetrazine tartrate
  - Benzphentamine/Didrex
  - Phentermine (Adepex-P)

- Sibutramine/Meridia (Category IV)
- Important
  - Short-term (8 to 12 weeks) drugs used for weight loss
  - Chemically and pharmacologically related to amphetamines
  - Mode of action
  - stimulate the release of norepinephrine and/or dopamine from storage sites in nerve terminals in the lateral hypothalamic feeding center
  - producing a decrease in appetite

- PK/PD
  - Lipid-soluble drugs, have wide distribution, cross blood–brain barrier
  - Metabolized by liver//excreted by kidneys
  - duration of action 4 to 6 hours
  - Have high risk of tolerance and dependence
  - Avoid using with patients with history of alcohol/drug dependence
  - Contraindicated in patients who abuse cocaine, methamphetamine, etc.

- Adverse drug reactions (ADRs)
  - CNS overstimulation:
    - agitation, confusion, insomnia, dizziness, HTN, headache, palpitations, arrhythmias, dry mouth, nausea/vomiting (n/v)
  - Sudden withdrawal of medication
    - in patients w/ long history
    - may cause withdrawal symptoms
  - Increases glucose uptake from skeletal muscles
    - caution in patients with diabetes

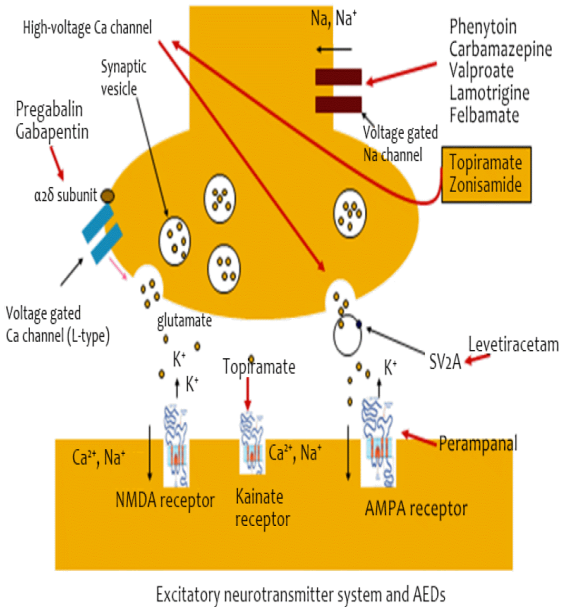
  - Drug interactions
    - Off-label use with selective serotonin reuptake inhibitors (SSRIs)
    - Prozac and phentermine (“Phen-Pro”)
    - Careful use with serotonergic medications:
      - increased risk for serotonin syndrome
    - Avoid monoamine oxidase inhibitors (MAOIs):
      - result in hypertensive crisis
    - Careful use with adrenergic blockers, insulin sulfonylureas, and phenothiazines
    - Lithium toxicity

ANTI-SEIZURE MEDICINES

- Typically grouped by their MOA/principal mode of action
  - Calcium current effectors
    - Ethosuximide, gabapentin and pregabalin
  - Gaba activity
    - Benzodiazepines, phenobarbital, tiagabine, vigabatrin
  - Glutamate receptor
    - Topiramate, felbamate, perampanel
  - Drugs affecting other MOA
    - Levetiracetam
      - Bind synaptic vesical protein SV2A

- Essentially, ALL antiseizure drugs act by one of these mechanisms:
  a. Stimulating an influx of chloride ions
     i. associated with the neurotransmitter gamma-aminobutyric acid (GABA)

b. Delaying an influx of sodium
c. Delaying an influx of calcium



Excitatory neurotransmitter system and AEDs

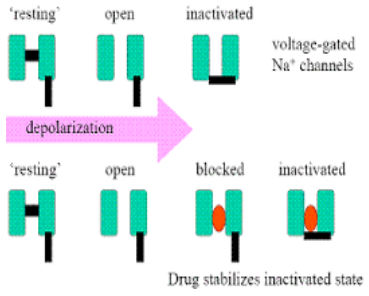
ANTICONVULSANTS

- Factors that may precipitate seizures
  - Sleep deprivation, high caffeine intake, hyperventilation, stress, hormonal changes, sensory stimuli, drug/alcohol use, infections, fever, metabolic disorders
- Anticonvulsant medications being used in the treatment of mood disorders

ANTICONVULSANTS: HYDANTOINS

MEDICATIONS IN THIS CLASS

- Ethotoin/Peganone
  - only available in 250 mg
- Fosphenytoin/Cerebyx
  - NOT for primary care
  - IM or IV dosing only
  - Given only for about 5 days
- Phenytoin/Dilantin
  - Nonlinear kinetics, many drugs alter concentration levels
  - Generic vs brand name may have effect on levels



- MOA: act on NA+ channels
- NA+ channels can normally exist in closed, open or inactivated states. AN activated gate is closed and NA+ ions cannot pass through the channel
- The channel activation gate opens, rapidly following depolarization and NA+ enters freely. Soon after opening an inactivation gate close preventing further NA+ getting into the cell.
- Hydantoin drugs stabilize and prolong the existence of the inactivated state and leads to sodium impedance

- PK/PD
  - Pharmacokinetics
    - Metabolism: Liver
    - strong CYP2C9 effects
    - Levels will increase
      - cimetidine, diazepam, acute alcohol intake, valproic acid, allopurinol
    - Decreases effects
      - barbiturates, antacids, calcium, chronic alcohol use
  - Pharmacodynamics
    - Works by stabilizing neuronal membranes and decreasing seizure activity by increasing influx of sodium ions across cell membranes in the motor cortex
    - Onset and duration vary
    - First-line treatment for tonic-clonic and partial complex seizures
    - Depresses neuron transmission in the nucleus ventralis anterior of the thalamus
    - Has ability to induce its own metabolism
    - Genetic testing of Asians

ADRS and DRUG INTERACTIONS

- Concurrent administration causes the decreased effect of:
  - Carbamazepine
  - Estrogens
  - Acetaminophen
  - Corticosteroids
  - Levodopa
  - sulfonylureas
  - cardiac glycosides

- Adverse Drug effects
  - there are many
  - ***Never give IV or IM in primary care setting***
  - Watch patients with liver and renal disease closely.

- Most common ADRs
  - Neuro
    - Nystagmus, dizziness, pruritus, paresthesia, headache, somnolence, ataxia, confusion
  - Cardiovascular effects
    - hypotension, tachycardia
  - Gastrointestinal (GI) effects:
    - n/v, anorexia, constipation, dry mouth, gingival hyperplasia
  - Genitourinary effects:
    - urinary retention, urine discoloration

RATIONAL DRUG SELECTION

- Nurse practitioner role: working with neurologist who has made diagnosis
- Used for grand mal and psychomotor seizures

PATIENT EDUCATION: DISCUSS RISK FACTORS FOR SEIZURES

- Report ADR
- Avoid driving if not seizure free for more than 1 year
- Oral hygiene

MONITORING

- Baseline laboratory values and plasma levels, along with thyroid-stimulating hormone (TSH)
- Need to assess OTC drugs: ibuprofen, antacids

ANTICONVULSANTS: CARBAMAZEPINES

Carbamazepine

- Tegretol, Tegretol XR, Carbatrol
- BLACK BOX WARNING
  - #1_____
  - #2_____

- Drug interactions:
  - Watch out for intake with _____
- Drug levels increase
  - with concurrent use of propoxyphene (Darvocet), cimetidine, erythromycin, clarithromycin, verapamil, hydantoins
- Decreases plasma levels of several drugs:
  - beta blockers, warfarin, doxycycline, succinimides, haloperidol

- Oxcarbazepine Trileptal
  - Chemical structure like carbamazepine
  - Only minimally affects CYP (advantage)

- ADRs
  - Depression of bone marrow
  - Liver damage, impairs thyroid function
  - Drowsiness, dizziness, blurred vision, n/v, dry mouth, diplopia, headache (HA)

- Monitoring
  - Baseline laboratory values: complete blood count, chemical panel, hepatic panel, TSH level
  - Patient education:
  - Teach about symptoms of bone marrow depression, CAREFUL use of medications, therapeutic dosing

ANTICONVULSANTS: SUCCINIMIDES

- Used for treatment of absence seizures in children and adults
- Ethosuzimide (Zarontin), methsuximide (Celontin)
- Pharmacodynamics
  - Suppresses seizures by delaying calcium influx into neurons
  - Decreases nerve impulses and transmission in the motor cortex
  - Absorbed in GI tract
- Pharmacokinetics:
  - metabolized in liver
- ADRs
  - GI most common; CNS: somnolence, fatigue, ataxia
  - Agranulocytosis, aplastic anemia, granulocytopenia

ANTICONVULSANTS: LAMOTRIGINE

- Lamotrigine (Lamictal)
  - Used in the adjunctive treatment of primary generalized tonic-clonic seizures and partial seizures in adults and children older than 2 years of age
  - Concurrent use with valproic acid, phenytoin
- Pharmacodynamics
  - Levels decreased by barbiturates, estrogens, phenytoin, mefloquine
  - Levels increased by alcohol, carbamazepine, CNS depressants, valproic acid
- Pharmacokinetics:
  - metabolized in liver and kidneys
- ADRs:
  - GI – mostly n/v, constipation; cardiovascular – chest pain, peripheral edema; CNS – somnolence, fatigue, dizziness, anxiety insomnia, headache, amblyopia, nystagmus; dermatological – rashes

- Patient education
  - adherence, avoidance of alcohol, avoidance of OTC drugs, adequate hydration, reporting any new drugs, reporting ADRs
  - Discussion of risk factors that contribute to seizures
  - Driving
  - Controversy about discontinuing medications after a few years of being seizure-free: neurologist to make decision

ANTICONVULSANTS: RUFINAMIDE

- Adjunctive treatment for Lennox-Gestalt syndrome (LGS)
- Modulates the activity of sodium channels
- Contraindicated in familial short QT syndrome
- ADRs: increased suicide risk, DRESS (drug rash with eosinophilia and systemic symptoms)
- Interactions: carbamazepine, phenobarbital, valproate