Neurodegenerative Disease

Part 2

ADHD
Narcolepsy
Epilepsy
Attention Deficit and Hyperactivity Disorder (ADHD)

Drugs tend to increase DA
ADHD Background

• Neurobehavioral development disorder in ~5% of people (4-12% of kids)
• Characterized by
  – Hyperactivity
  – Inattention
  – Impulsiveness
• Complex interaction of genes
  – DA transport proteins (too many DAT)
    • Leads to DA deficiency

Fe^{++} commonly deficient in ADHD; Fe^{++} required for DA, NE and 5-HT synthesis
Drugs used to treat ADHD

**Psychostimulants**

- **PO** Dextroamphetamine (Adderall, etc.) C-II
- **PO, TD** Methylphenidate (Ritalin, Concerta) C-II

**Selective NE reuptake inhibitors**

- **PO** Atomoxetine (Strattera) *Do not crush ❌*

**Off label**

- **PO** Donepezil (Aricept) ✗
- **PO** Clonidine (Catapres)
Dextroamphetamine (Adderall) C-II
Also: Dextedrine Spansules, Dextrostat, ProCentra

• A 3:1 ratio of d-to l-amphetamine
• Noncatechololamine sympathomimetic
  – Blocks DA & NE reuptake
  • not with MAOIs
• Potential to trigger psychosis

Psychostimulant indicated for ADHD & Narcolepsy

Monitor
1. Baseline BP/HR
2. Ht/Wt in kids

☐ Pot’l for abuse

PO titrate over 2-4 weeks
Don’t give after 6 pm to avoid insomnia

☐ Pot’l for sudden death or serious CV event
Methylphenidate (Ritalin) C-II

Other trade names: Concerta, Daytrana, Focalin, Metadate, Methylin

- Mild CNS stimulant
- NO MAOIs
- May cause
  - Sudden death, serious CV event, or psychosis (including bipolar disorder)
  - Stunted growth
  - Blurred vision

PO, TD (apply in a.m., remove 9 hours later)
Individualize and periodically give a “drug holiday” to assess need for drug

Monitor
1. Baseline BP/HR
2. Ht/Wt in kids
3. CBC with differential
4. Platelets annually

□ Pot’l for abuse
Atomoxetine (Strattera) 🚑

- **Mechanism**
  - Selective NE reuptake inhibitor (SNRI)

- **Indication**
  - ADHD

- **ADRs**
  - CNS: aggression, bipolar emergence, psychosis, sedation, insomnia, priapism/erectile dysfunction
  - CV: HT, tachycardia, orthostasis
  - Angioedema, rash
  - Urinary retention
  - Dry mouth, nausea, constipation
  - Hot flush

  - **PO**
    - No need to taper off; give a.m. and p.m.

  - **Monitor**
    1. Baseline BP/HR
    2. Ht/Wt in kids
    3. Behavioral changes

  - **Suicide**

  - **No concurrent MAOIs!!**

  - **Like all CNS stimulants, it can cause sudden death (stroke, MI) and precipitate psychosis and or mania.**

  - **No**
Narcolepsy

Psychostimulant

Xyrem (γ hydroxybuterate) is the only drug with two DEA control schedule listings (C-I and CIII). It is used to treat catalepsy (sudden muscle weakness).
Modafinil (Provigil, Nuvigil) C-IV

• Mechanism - binds to DAT ↓D reuptake?

• Indication
  – To improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder.

• ADRs

  SJS, etc., multiorgan hypersensitivity reactions

  CNS: mania, delusions, hallucinations, suicidal ideation, aggression - ESPECIALLY in psych patients

  Federally controlled substance

Not approved for any indication in pediatric patients!!
Epilepsy
Anticonvulsant Drugs
AKA AEDs
or Neuromodulators

Drugs tend to stabilize ion channels
Used to treat seizures caused by:
  Epilepsy
  Fevers (febrile seizures)
  Pre eclampsia or eclampsia
Overview

• Epilepsy - CNS disorder characterized by periodic and unpredictable seizures.
  – **Partial**
    • 1 hemisphere
  – **Generalized**
    • Both hemispheres affected
    • Ideopathic or Symptomatic
  – **Post traumatic**
    • Blow to head, wake up with epilepsy

**ADRs common to AEDs**
• Altered excitability
  • Seizures
  • Arrhythmias
• Suicidal ideation
• Sedation
• Weakness
• ↓ steroid hormones
• Titrate on/off

**Monitoring -**
AEDs typically require a lot of monitoring
Classification

• Partial *(1 hemisphere)*
  – Originate in a clearly defined location
    • AKA: Focal seizures
    • May spread and become Generalized
  – Simple Partial
    • 60% of seizures, no loss of consciousness
    • Affect motor or sensory parts of brain
  – Complex partial
    • Altered consciousness
    • Often preceded by an aura
  – Marching seizures

Also, rarely, autonomic, psychic or aphasic
Generalized (both hemispheres)

– Tonic-clonic - “Grand mal” - tonic (contracted) to clonic (muscle spasms) to postictal (dazed)

– Absence - “Petit mal” - abrupt loss of consciousness

– Myoclonic - sudden, uncontrollable jerks (think hiccups)
  • Negative myoclonus = sudden muscle relaxation
  • Positive myoclonus = sudden contraction
  • May be associated with ALZ, MS, PD, stroke, spinal cord injury, liver or kidney disease or lipid storage diseases.

– Clonic - repetitive, rhythmic contraction of muscle held in stretched state; a deep tendon reflex
  • Commonly associated with MS

– Atonic - sudden relaxation of all muscles (“drop seizure”)

PHRM 203 - A Beale  Neurodegenerative Diseases, ADHD, Epilepsy
Carbamazepine (Tegretol)

- Similar structure to TCAs
- Mechanism - \( \otimes \) voltage-gated \( \text{Na}^+ \) channels
- Interactions - POTENT \( \uparrow \) P450
- Indications
  - Tonic-clonic & partial seizures
  - Trigeminal neuralgia ("tic douloureux")
  - Bipolar disorder
- ADRs
  - Anticholinergic activity
  - Teratogen (spina bifida)
  - Seizures, arrhythmias (heart block)
  - Multiorgan hypersensitivity

⚠️ \( HLA-B \ 1502 \ ± \ SJS, TENS \)

⚠️ Aplastic anemia & agranulocytosis

Avoid use in patients with hepatic porphyria

Available as rectal and enteric (but sticks to PVC tubing used for NG tubes!)

Lots of off label uses: PTSD, ADHD, schizophrenia, explosive behavioral disorders, pain...

Common issues: Diarrhea, nausea, vomiting, fluid retention, rash, blurred vision, sedation, headache….

PO
Divalproex (Depakote), Valproate (Depacon), valproic acid (Depakene)

- Good GI absorption, active & inactive metabolites
- \(\oplus\) GABA synthesis, \(\downarrow\) GABA metabolism \(\otimes\) Na\(^+\) channels

**Indications**
- T-C type seizures, myoclonus, complex partial & absence seizures, bipolar disorder, migraines

**Interactions:**
- P450 \(\otimes\) → alter drug metabolism
- Strongly PP bound → alter drug availability (aspirin!)

**ADRs**
- Weight gain, hair loss, bone loss, nausea, vomiting, tremor

- \(\square\) Hepatotoxic
- \(\square\) Teratogenic (no brain)
- \(\square\) Pancreatitis

Available as rectal and enteric

PO

Do not crush ✗

Valproate - IV

Valproic acid - PO

P450 ↓

Hepatotoxic

Teratogenic (no brain)

Pancreatitis
Ethosuximide (Zarontin)

- CCB’er in thalamic neurons
- Interactions: valproate $\otimes$ ethosuximide metabolism & haloperidol alters seizure pattern
- **Indications**
  - Absence seizures (drug of choice).
- ADRs
  - blood dyscrasias, liver/kidney function changes, Lupus, possible teratogen. Also nausea, vomiting, sleep disturbances, hyperactivity, drowsiness.

Clonazepam (Klonopin) قبول like clorazepate
- Benzodiazepine with sedation side effects, may be used to treat absence, myoclonic or atonic seizures.
Gabapentin (Neurontin) 🌵

- Unknown mechanism (it’s a GABA analog)
- As dose increases, bioavailability decreases!

Indications
- Postherpetic neuralgia and partial seizures
- Used off label: bipolar disorder, to control aggression and agitation in elderly with dementia, alcohol withdrawal, anxiety disorders

ADRs
- Emotional lability and hyperactivity, or sedation

Pregabalin (Lyrica) C-V 🚚

- Unknown mechanism – 2-3 X more potent than Gabapentin

Indications
- Postherpetic and diabetic neuropathic pain (neuralgia)
- Partial onset seizures
- Fibromyalgia
- May cause weight gain, dry mouth, blurred vision, sedation, dizziness....
Lamotrigine (Lamictal)

**Indications**
- Partial, Grand mal and Lennox-Gastaut syndrome epilepsy
- Bipolar disorder
- Used off label for MDD

**Mechanism**
- ⊗ Voltage-gated Na\(^+\) channels

**Other drugs indicated for partial seizures**

**Clorazepate (Tranxene)**
- Like clonazepam
- Metabolized to diazepam, indicated as anxiolytic, partial seizures, & alcohol withdrawal syndrome

**Felbamate (Felbatol)**
- Drug of last choice
- Unique: NMDA blocker, but potentially fatal (aplastic anemia/liver failure)
Phenobarbital (Luminal, Gardenal) C-IV & Primidone (Mysoline)

- **Active metabolites** (*Primidone metabolized to phenobarbital*)
  - Tolerance and dependence issues
- **⊕ GABA\textsubscript{A} receptor (↑inhibition)**

**Indications**
- Grand mal & partial seizures. *Status epilepticus*
- Sedative, short term hypnotic

**Interactions and ADRs**
- P450 induction → alter drug metabolism
- Impaired CNS function → ataxia, dizziness, drowsiness, cognitive impairment, respiratory depression. Hyperactivity may be seen in kids.
Phenytoin (Dilantin) & fosphenytoin

- Fosphenytoin more H₂O soluble
- Mechanism - ⊗ voltage-gated Na⁺ channels
- Interactions – LOTS; t ½ ~ 24 Hr.
- Use during PREGNANCY
  - ↑Seizure frequency in pregnant women
  - Fetal effects (neonatal coagulation defects, malignancies, congenital malformations...)
- P450 induction → alters drug metabolism
- Indications
  - Tonic-clonic & complex partial seizures
  - Status epilepticus
  - Prevention of seizures during neurosurgery

Off label: neuropathic pain, digoxin intoxication, antiarrhythmic

PO, IV, IM (last resort)

Available as enteric suspension, but PPTs out in dextrose (eg D5W)

P450 ↑

Suicide

IV slowly
Phenytoin (Dilantin) ADRs

- IV Must be administered slowly to avoid cardiotoxicity
  - Contraindicated in sinus bradycardia, etc, due to ↓↓ ventricular automaticity
- Impaired CNS function → ataxia, diplopia, nystagmus, slurred speech, delirium, psychosis, dizziness, twitching
- Peripheral Sensory polyneuropathy with long term use
- ⊗ Folate metabolism → megaloblastic anemia & birth defects
- ⊗ Vit D metabolism & GI Ca++ absorption → osteomalacia
- ⊗ collagen metabolism → gingival hyperplasia
- ↑ Hirsutism and coarsening of facial features
- Lymphadenopathy (hyperplasia, lymphoma, Hodgkin’s...) & hemopoietic conditions (thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia)
- Fever, rash (including SJS)
- Extravasation injuries to soft tissues
- Hyperglycemia

Available as a solution, but sticks to the PVC tubing used in NG tubes
Topiramate (Topamax)

• **Mechanism**
  - ⊗ Voltage-gated Na\(^+\) channels
  - ⊕ GABA receptors
  - ⊗ Glutamate receptors
  - Θ Carbonic anhydrase

• **Indicated for:**
  - Monotherapy for grand mal or partial onset seizures
  - Adjunct for Grand mal, partial onset epilepsy & Lennox-Gastaut syndrome
  - Migraine
  - Used off label for PTSD, neuropathic pain, and to prevent alcoholics from drinking

• **ADRs**
  - Cognitive impairments common (can’t find words)

Other common adjuncts
- Tiagabine (Gabitril)
- Vigabatrin (Sabril)
- Zonisamide (Zonegran)
- Levetiracetam (Keppra)

Available as an enteric

PO

Do not crush
Therapeutics:  *Status epilepticus*

- **Diazepam** or **lorazepam** (less lipophilic)
  - IV
- **Phenytoin** or **fosphenytoin**
  - Given IV after benzodiazepine, longer $t_{1/2}$.
- **Phenobarbital** or **General Anesthesia**
  - Used if other treatments fail
  - Induces “Phenobarb Coma”

*Most available in rectal and/or enteric formulations*