CNS1 Epilepsy (McAuley) Alzheimer's disease (Emptage) Pcol (Hoyt K) MC (Adu) Ceutics (Cocucci) Synaptic/BBB (Sparreboom)	CNS2 Depression (Romstadt) Anxiety (Barnes) Sleep (Hall) Pcol (Hoyt K) MC (Li) Ceutics (Cocucci)	CNS3 Parkinson's disease (Emptage) Schizophrenia (Maguire) Bipolar (Romstadt) ADHD (Novak) Pcol (Hoyt K) MC (Adu) Ceutics (Cocucci)
CNS4 Pain (Kullgren) Palliative (Kullgren) Headache (Shneker) Substance Use (Schmuhl) Toxicology (Stevenson) Pcol (Hoyt K) MC (Li) Ceutics (Cocucci)	MS Osteoporosis (Woods) RA, PA (Nahata) OA, Gout, Fibro (Nahata) SLE Lupus (Silva) MS (Kullgren) Pcol (Hoyt D) MC (Li)	ID Endocarditis (Groff) Meningitis (Ramey) Hepatitis (Tharp) HIV (Pauvlinch) Invasive Fungal Infections (Pai) Community Acquired Viral Infections (Hanks) COVID-19 (Smith) Pcol (Hoyt D) MC (Fuchs) Ceutics (Baker)

Alzheimer's

Pathophysiology

Dementia: *gradual* onset progressive cognitive impairment; profound loss of short and long-term memory; long-term condition; can be permanent
Alzheimer's disease (AD): characterized by gradual decline in cognition over period of years; neural specific pathologic process; prevalence increases with age
- prevalence increases drastically with age: ~5% at 65yo; >30% at >85yo; can occur in younger but uncommon

Delirium: *acute* cognitive impairment with clouded sensorium; difficulty with attention; may have hypersomnolence

Pathogenesis of Alzheimer's disease
Localized loss of neurons initially in hippocampus, basal forebrain, temporal frontal cortex; eventually, overall atrophy of tissue throughout brain

Memory formation at synaptic level
- hippocampus is one critical brain region for learning and memory
- phenomenon of Long-Term Potentiation (LTP): synaptic plasticity (strengthening in response to learning)
  a) LTP induction: LTP induction leads to activation of NMDA receptors
  b) LTP consolidation (spine morphogenesis): Ca influx through NMDA receptors leads to trafficking of glutamate receptors into spines
  c) LTP maintenance (spine stabilization): increase in AMPA receptors in dendritic spines enhances responsiveness to glutamate; contributes to glutamate-induced maintenance of spines by stabilizing actin filaments
- glutamate-excitatory transmitter: important role of glutamate receptors (both ioniotropic):
  - AMPA: respond to glutamate at resting membrane potentials; only permeable to Na; short lasting responses
  - NMDA: respond to glutamate at depolarized membrane potentials; permeable to Na and Ca; longer lasting responses
    - Mg blocks channel at polarized potentials; when depolarize the channel Mg is relieved, glutamate able to activate NMDA receptor allows influx of Na Ca

The basal forebrain nuclei are important in cognition and learning
- acetylcholine (ACh) is a neurotransmitter with great influence on memory
- evidence: muscarinic cholinergic antagonists (atropine, scopolamine) lead to memory deficits at low conc, delirium at high conc; disruption of memory/concious

Synthesis and degradation pathway of ACh: acetylcholinesterase hydrolyzes acetylcholine to choline
- nicotinic (nAChR)-ionotropic (Na Ca permeable – excitatory)
- muscarinic (M)-metabotropic (G-protein coupled – neuromodulatory)

Cholinesterases
- butyrylcholinesterase (BuChE): nonselective (acts on multiple choline esters), function not known; mainly found in peripheral tissues and glial cells
  - measured increases of BuChE in AD associated with plaques and tangles due to shift in enzyme dependence of ACh metabolism in AD (bigger BuChE role?)
- acetylcholinesterase (AChE): selective for acetylcholine, important for terminating cholinergic transmission; more in brain than BuChE
  - isoforms: tetramer 'G4' and monomer 'G1'; greater loss of G4 isoform with AD progression

Pharmacology

NMDA receptor antagonist

memantine (Namenda)

- moderate uncompetitive affinity
  - uncompetitive because requires receptor to be activated in order to block channel; so you need glutamate to bind in order to open the channel so it can bind to its binding site within the channel; requires binding of the agonist (glutamate) and activation of channel in order to enter and block
- theory: 'excitotoxicity' produced by excessive amounts of glutamate is hypothesized to contribute to neuronal cell death and dysfunction in AD

Memantine: Glutamate, the primary excitatory amino acid in the CNS, may contribute to the pathogenesis of Alzheimer disease (AD) by overstimulating various glutamate receptors leading to excitotoxicity and neuronal cell death. Memantine is an uncompetitive antagonist of the N-methyl-D-aspartate (NMDA) type of glutamate receptors, located ubiquitously throughout the brain. Under normal physiologic conditions, the (unstimulated) NMDA receptor ion channel is blocked by magnesium ions, which are displaced after agonist-induced depolarization. Pathologic or excessive receptor activation, as postulated to occur during AD, prevents magnesium from reentering and blocking the channel pore resulting in a chronically open state and excessive calcium influx. Memantine binds to the intra-pore magnesium site, but with longer dwell time, and thus functions as an effective receptor blocker only under conditions of excessive stimulation; memantine does not affect normal neurotransmission.

Cholinesterase inhibitors

- can produce small short-term cognitive imporvements in some patients; generally modest improvements in memory, coginition, overall QoL

donepezil (Aricept)

- reversibly and noncompetitively inhibits centrally-active acetylcholinesterase; results in increased concentrations of ACh available for synaptic transmission
- selective for AChE > BuChE (400:1)

Donepezil: Alzheimer disease is characterized by cholinergic deficiency in the cortex and basal forebrain, which contributes to cognitive deficits. Donepezil reversibly and noncompetitively inhibits centrally-active acetylcholinesterase, the enzyme responsible for hydrolysis of acetylcholine. This appears to result in increased concentrations of acetylcholine available for synaptic transmission in the central nervous system.

rivastigmine (Exelon)

- inhibits both AChE and BuChE
- greater potency for G1 > G4 AChE
  - may afford a more prolonged treatment than other cholinesterase inhibitors?
- prolonged inhibition ('pseudo-irreversible')

galantamine (Razadyne)

- plant alkaloid
- more selective for AChE > BuChE (50:1)
- also positive allosteric modulator of nicotinic acetylcholine receptors

main pathological features of AD comprise amyloid plaques, neurofibrillary tangles and a loss of neurons (particularly cholinergic neurons of the basal forebrain)

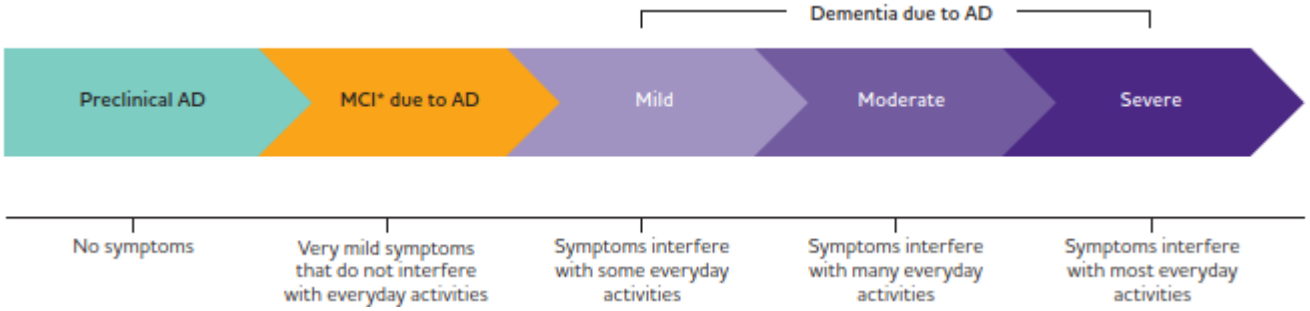
Therapeutics

Clinical Presentation/Warning Signs
1. **Memory loss** more than typical forgetfulness without remembering later
2. **Difficulty** performing familiar **everyday tasks** (preparing a meal or grooming)
3. Problems with **language**: forgetting simple words or substituting unusual words
4. **Disorientation** to time and place: may forget where they are and/or how they got there
5. **Poor or decreased judgment**: dress without regard to weather or falling prey to scams
6. Problems with **abstract thinking**; not just difficulty balancing a check book, but forgetting what the numbers represent
7. **Misplacing things** in unusual places; such as placing an iron in a freezer
8. **Changes in mood or behavior**; rapid mood swings with no apparent reason why
9. **Changes in personality**; extreme confusion, suspicion, or fearfulness
10. **Loss of initiative**, passivity and **loss of interest** in usual activities

Types of Dementia

Alzheimer's disease: Accounts for 60-80% of all cases
Vascular dementia from Cerebrovascular disease: About 5-10% show vascular dementia alone, but many can have both vascular and Alzheimer's dementia
Lewy body disease (LBD): About 5% have LBD alone –accumulation of Alpha-synuclein in the cerebral cortex
Fronto-temporal lobar degeneration (FTLD): Include behavioral-variant FTLD, primary progressive aphasia, Pick's disease, corticobasal degeneration and progressive supranuclear palsy
Hippocampal sclerosis (HS): Often found in the "oldest-old," those over 85 years of age
Mixed pathologies: Studies have suggested that more than 50% of the cases of dementia may have more than one cause

Progression of Alzheimer's disease



Mild cognitive impairment*
Problems with memory, language or other essential cognitive functions that are severe enough to be noticed by others and are reflected on cognitive tests, but **are not severe enough to interfere with daily life**.

Dementia
Progressive global deterioration of cognitive abilities in multiple domains, including **memory**, and at least 1 additional area:
- Learning - Orientation - Language - Comprehension - Judgment
- **Severe enough to interfere with daily life**

DSM-5 criteria for "Major Neurocognitive Disorder" (previously dementia)
A. Evidence of **significant cognitive decline** from a previous level of performance in one or more cognitive domains*:
- Learning and memory - Language - Executive function - Complex attention - Perceptual-motor - Social cognition
B. The cognitive deficits **interfere with independence in everyday activities**. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.
C. The cognitive deficits do **not** occur exclusively in the context of a **delirium**
D. The cognitive deficits are **not better explained by another mental disorder** (eg, major depressive disorder, schizophrenia)

Differential Diagnosis of Alzheimer's disease
- benign senescent forgetfulness - vascular dementia - drug induced (benzos, antipsychotics, anticholinergic side effects) - normal pressure hydrocephalus
- infectious disorders - depression - Parkinson's disease - CV disorders - thyroid disorders - progressive supranuclear palsy

Pathology
Affects neurons in the basal forebrain: amygdala, hippocampus, cerebral cortex
Neuronal loss: most known about the deficits in cholinergic neurons; decreased prevalence of one of the glutamate receptors (NMDA)

Neurofibrillary Tangles within the neuron cell itself; stabilizing Tau proteins/molecules start to clump together, can't stabilize microtubule = degradation of neuron
Amyloid Plaques in the extracellular space surrounding neurons
- amyloid precursor protein (APP) cleaved to beta amyloid which is abnormal protein which can cause the clumping to happen in extracellular space
- for abnormal Beta Amyloid protein to be produced from APP, **both Beta and Gamma secretases** have to be involved with cleave of APP
- if Alpha secretase cleaves APP, the Beta Amyloid is not produced; (research for inhibitors are being explored)

Etiology
Risk factors: age, female>male, head trauma, toxins (low IQ and small head/brain)
Familial – genetic component: two alleles for apolipoprotein E4, risk of AD is much higher

Diagnosis
- definitive (can't really do)
- possible (most people)
- probable: brain imaging (PET to look for Beta Amyloid accumulation; MRI); biomarkers; neuropsychological testing, other tests
  - Mini-Mental State Examination (MMSE)*
    - 20-24: mild disease; forgetfulness, work and social impairment, mild anxiety
    - 10-19: moderate disease; concentration, complex skills decline, flax affect and withdrawal
    - <10: severe disease; unable to recall or recognize people/places, requires assistance with ADLs
    - 0: profound
  - Mini Cog Test: give patient 3 words to remember, draw picture of face of clock (ten past 11), ask patient to recall 3 words
    Scored as number of recalled words and normal/abnormal clock draw:
    - 3: negative screen for demential (no need to score CDT)
    - 1-2 and normal CDT: negative for CI
    - 1-2 and abnormal CDT: positive for CI
    - 0: positive for CI

Treatment
Cholinesterase Inhibitors
GI side effects are often dose limiting; **maximizing the dose is important for most clinical benefit**
All agents increase gastric acid secretion and therefore should be monitor for **GI bleeding**
Agents also should be monitored for effects on the SA and AV nodes that might cause **bradycardia or syncope**
SE: GI upset (NVD), bradycardia, weight loss

donepezil (Aricept)
use: mild, moderate, severe
dose: 5mg/day for 6 weeks then 10mg/day (usually dosed once daily in the evening)
formulation: 5mg 10mg 23mg tablet, Aricept ODT
SE: GI upset, bradycardia, weight loss; rare cases of Neuroleptic Malignant Syndrome and Rhabdomyolysis
August 2010 FDA approved a 23mg once daily strength for moderate to severe AD
  Appears to have added benefit, but also higher incidence of GI side effects including weight loss; must be established on 10mg for 3 months before trying 23mg

rivastigmine (Exelon)
use: oral: mild to moderate patch: mild to moderate, severe; Parkinson dementia
dosing: 1.5mg bid increase by 1.5mg bid after 2weeks up to 6mg bid patch: 4.6mg/24hr patch qday after >4weeks increase to 9.5mg/24hr patch qday
  - conversion <6mg/day capsule = one system of 4.6mg/24hrs patch; 6-12mg/day capsule = 9.5mg/24hr patch
formulation: 1.5mg 3mg 4.5mg 6mg capsule; 2mg/ml solution patch: 4.6mg/24hr 9.5mg/24hr
SE: GI upset (more than donepezil); bradycardia, weight loss, disseminated allergic dermatitis with oral and patch
pearls: give with meals; slow/cautious titration renal/hepatic or low body weight patch: rash, rotate sites; fewer SE; max 4.6mg/d mild-mod liver or low weight

galantamine (Razadyne)
use: mild to moderate
dosing: 4mg bid, after 4 weeks increase to 8mg bid then again to 12mg bid
formulation: 4mg 8mg 12mg tab; 4mg/ml solution; 8mg 16mg 24mg ER capsules
SE: GI upset, bradycardia, weight loss; skin reactions including Stevens-Johnson Syndrome
pearls: give with meals; moderate renal/hepatic impairment max 8mg bid or 12mg ER qday; do not use in severe renal/hepatic impairment

NMDA antagonist calcium influx from NMDA receptor activate by glutamate → cell death
memantine (Namenda)
use: moderate to severe, with some info on vascular dementia
SE: well tolerated; severe renal impairment max 5mg bid or 14mg XR qd
dosing: 5mg po qd; increase at minimum 1 week intervals in 5mg increments to 10mg/day (5mg bid), 15mg/day, and 20mg/day (10mg bid); to target 20mg/day
Namenda XR 7mg 14 21 28; Solution 2mg/mL
Namzaric 24hr ER capsule: memantine 14mg/donepezil 10mg or memantine 28mg/donepezil 10mg

Mild to Moderate AD
Initial therapy → disease progression: consider higher dose or switch to different ChEI and follow moderate to severe dosing
  - donepezil 5mg qday; titrate after 6 weeks to 10mg qday
  - rivastigmine tab 1.5mg bid; titrate every 2 weeks to 6mg bid
  - rivastigmine patch 4.6mg qday; titrate every 4 weeks to 9.5mg qday
  - galantamine tab 4mg bid; titrate after 4 weeks to 8mg bid, then to 12mg bid
  - galantamine ER cap 8mg qday; titrate every 4 weeks to 16mg qday, then to 24mg qday

Moderate to Severe AD
Initial therapy → monitor and evaluate therapy every 3-4 months and titrate dose → disease progression: consider switch or higher dose → discontinue therapy
  - donepezil 5mg qday; titrate after 6 weeks to 10mg qday
  - rivastigmine (patch) 4.6mg qday; titrate every 4 weeks to 9.5mg qday
  - memantine 5mg qday; titrate to 10mg bid or memantine XR 7mg qday; titrate every week to 28mg qday
  - combination ChEI + memantine 7mg bid or 10mg ER qday; titrate to 10mg bid or 28mg ER qday
Discontinue therapy when all cognitive function and functional abilities are lost at terminal stages of AD

Behavioral and Psychological Symptoms of Dementia (BPSD): >80% experience agitation ~40% experience aggression

Behaviors more response to medical treatment: hyperactivity, physical/verbal agitation, psychotic or delusional symptoms, depressive symptoms, hallucinations
Behviors less responsive to medical treatment: wandering, public disrobing, hoarding/hiding objects, repetitive questioning, isolativeness, social inappropriateness

Behavioral Problems
Describe the symptoms
Investigate the causes
Create a treatment plan: nonpharm interventions, consider ChEI, consider pharmacologic therapy
Evaluate interventions

Nonpharm (behavioral) interventions: Using a gentle calm approach to the patient, Giving reassurance when needed, Empathizing with the patient's concerns, Using distraction and redirection, Maintaining daily routines, Providing daytime activities, Daily exercise routines, Avoiding overstimulation, Using familiar decorative items in the living area, fidget blanket
- newer ideas: aromatherapy, music therapy, pet therapy, massage/touch therapy, exercise

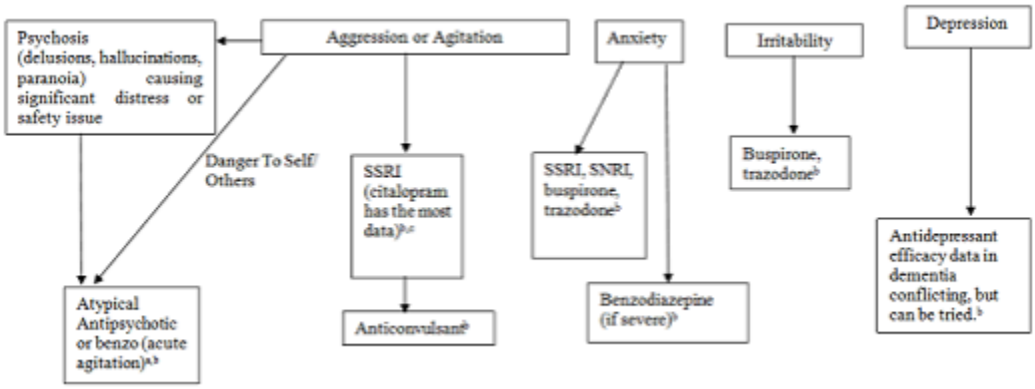
Pharmacological options
anxiety (excessive worrying, sleep disturbances, rumination): trazodone, buspirone, SSRI
depression (withdrawal, loss of appetite, irritability, restlessness, sleep disturbances): trazodone, SSRI
general agitation (repeated questions, wandering, pacing): redirecting activity, safety proofing
psychotic behaviors (delusions often of theft, hallucinations less common, misperceptions): atypical antipsychotics (paranoid sxs), SSRI (withdrawal, tearfulness)
aggressive behaviors (physical/verbal aggressiveness, excessive yelling, manic features): divalproex or carbamazepine, +/- atypical antipsychotic; DXM/quinidine

Antipsychotics
Target symptoms: psychosis: hallucinations, delusions, suspiciousness; disruptive behaviors: severe agitation, severe aggression
BBW cerebrovascular effects (TIAs/stroke); very cautious with use due to increased mortality

aripiprazole	10-15mg	maintenance 30mg (max)
olanzapine	2.5mg	maintenance 5-10mg
quetiapine	25mg	maintenance 100-400mg
risperidone	0.25mg	maintenance 0.5-2mg

Antidepressants
Target symptoms: poor appetite, insomnia, hopelessness, anhedonia (inability to feel pleasure), withdrawal, suicidal thoughts, agitation, anxiety

citalopram	10mg	maintenance 10-20mg
escitalopram	5mg	maintenance 10mg
fluoxetine	10mg	maintenance 10-20mg
paroxetine	10mg	maintenance 10-40mg
sertraline	12.5mg	maintenance 150mg (max)
mirtazapine	15mg	maintenance 15-30mg
trazodone	25mg	maintenance 75-150mg



Anticonsulants
Target symptoms: agitation or aggression

carbamazepine	100mg	maintenance 300-600mg
valproic acid	125mg	maintenance 500-1500mg

Other agents for symptomatic treatment
selegiline: anxiety and agitation
beta blockers: aggressive behaviors, especially sexually
gabapentin, lamotrigine, methylphenidate
dextromethorphan and quinidine (Neudexta): for pseudobulbar affect in patients with MS and ALS (off label agitation/aggression in AD); QTc prolongation risk
- 20mg/10mg qday for 7 days then increase to 20mg/10mg bid

Potential targets to interfere with disease process in AD
- inhibition of Amyloid Beta production: decrease Beta and Gamma secretases, increase Alpha secretase
- inhibition of Amyloid Beta plaques formation: decrease Aβ aggregation/fibrillation
- promotion of Amyloid Beta degradation and clearance
- inhibition of NFT formation; decrease Tau hyperphosphorylation/aggregation
- reduction of neuroinflammation
- reduction of oxidative stress; decrease reactive oxygen species

Medications which have been explored
- anti-inflammatory drugs, gingko biloba, estrogens, medium chain triglycerides (caprylidene and coconut oil), vitamin E antioxidant
- inhaled insulin (ALZ affected brain areas express insulin receptors as well as reduced insulin levels and signaling): SNIFF trial 2018 no beneficial effect on cog
- metformin: potentiate role of insulin resistance on ALZ development; some data to suggest beneficial increasing functioning in DM patients with AD
- solanezumab: monoclonal IgG directed against mid-domain of Aβ peptide; EXPEDITION-3 trial missed primary end point, no longer persued by Eli Lilly
- other trials: https://www.alzforum.org/therapeutics http://doi.org/10.1002/trc2.12050 for pipeline development

Epilepsy

epilepsy: recurrent unprovoked seizures (>2)
seizures: sudden, uncontrollable electrical discharges in normal brain activity
- partial (75%): simple, complex
- generalized (25%): absence, atonic, tonic, myoclonic, tonic-clonic

Partial Seizures (Local)

Simple Partial Seizures
- aka Auras
- consciousness not impaired (only one); still alert, memory intact
- diverse symptoms: motor (head turn), sensory (numbness), autonomic (sweating), psychic (hallucinations)
- may proceed to complex partial or generalized tonic-clonic

Complex Partial Seizures
- most common type
- consciousness and memory impaired
- automatisms (having nonsensical, repetitive movements/motions)
- last 30 seconds to 3 minutes; lethargic and confused post-ictally
- presentation/anatomy: drop attacks (frontal lobe), numbness (parietal), visual disturbances (occipital), oral automatisms (temporal lobe)
  - very little intrapatient variability; consistent symptoms with patients with epilepsy
- can proceed to generalized tonic-clonic

Generalized Seizures

Generalized Tonic-Clonic (*Grand Mal)*
- loss of consciousness; most dramatic seizure
- tonic (stiffening) – fall – cry out (air being forced through vocal chords) – clonic (contractions/relaxations)
- lasts 1 to 2 minutes
- physical signs: like intense workout, tongue biting, incontinence (bladder/bowel)
- postictal: lethargy, confusion/agitation, soreness
- if patient comes through simple to complex to generalized tonic-clonic it's called secondarily generalized tonic-clonic (otherwise generalized onset tonic-clonic)
- treatment: valaproate, lamotrigine, carbamazepine, topiramate, levetiracetam

Absence *(Petit Mal)*: brief (2-15 seconds) episodes of staring, unable to respond; onset 4-14yo, can resolve by 18yo; treatment: ethosuximide, valproate
Myoclonic: brief, bilateral jerk of neck, shoulders, or legs
Tonic: brief (<20 seconds) bilateral stiffening of body, arms, or legs
Atonic: brief(<15 seconds) sudden loss of muscle tone, drop things; hallmark of Lennox-Gastaut Syndrome

Status epilepticus
- seizure lasting >30 minutes or No Recovery – life threatening
- many patients no previous history of epilepsy
- causes: withdrawal or noncompliance with AEDs, metabolic disturbances, cerebral lesions
- convlusive or nonconvulsive
- treatment: IV benzos, (fos)phenytoin, phenobarbital, etc.

What should be done for someone having a seizure?
- lay them down and turn head to side (aspiration/vomit), loosen clothing and remove glasses, prevent further head trauma
- don't put anything in mouth or be combative

AEDs

phenytoin (PHT, Dilantin)
use: partial and generalized
pk: inducer; saturable metabolism
toxicity: nystagmus, ataxia, gingival hyperplasia, osteomalacia (vitamin D deficiency, decreased bone density typically after 2 years)
pearls: need small dosage adjustments (especially after 300mg)

carbamazepine (CBZ, Tegretol, Carbatrol, Equetro)
use: partial > generalized; can make absence seizures worse
pk: inducer 3A4, auto-induction (increase dose in 2-4 weeks to see shortening of half-life; 30-40hr HL to 20-25hr HL)
toxicity: dizziness, diplopia (double vision), leukopenia (monitor WBC), osteomalacia
pearls: may worsen some generalized seizure types; use outside of epilepsy (maintenance bipolar disorder, pain for trigeminal neuralgia)

oxcarbazepine (OXC, Trileptal, Oxtellar XR)
use: partial > generalized
pk: can be induced and inhibited; can inhibit minor pathway of phenytoin; can induce OCs above 1200mg/d
toxicity: dizziness, diplopia, ataxia, hyponatremia
pearls: monitor sodium

valproic acid (VPA, Depakote, Depakene, Depakote ER)
use: partial and generalized
pk: inhibitor
toxicity: "bald, fat, shaky, bruising": sedation, NV, weight gain (big, 50-100lbs), hair loss, tremor, thrombocytopenia
pearls: not for woman childbearing age; use outside of epilepsy (maintenance of bipolar disorder; migraine prophylaxis)

lacosamide (LCM, Vimpat)
use: partial
pk: no pk DI per package insert but metabolized 3A4, possibly PD
toxicity: indistinguishable, pretty bland toxicity profile; diplopia, headache, dizziness, nausea
pearls: IV formulation

lamotrigine (LTG, Lamictal)
use: partial and generalized
pk: can be induced and inhibited; estrogen in OCs can induce LTG which increases clearance leading to breakthrough seizures; pregnancy can increase clearance
toxicity: sedation, diplopia, ataxia, nausea; rarely cause life-threatening rash (Stevens-Johnsons Syndrome, Toxic Epidermal Necrolysis)
pearls: slow taper (especially valproate); use outside of epilepsy (maintenance of bipolar disorder)

topirmate (TPM, Topmax, Trokendi, Qudexy XR)
use: partial and generalized
pk: can be induced; can induce OC metabolism (>200mg/d)
toxicity: difficulty concentration, word-finding abilities, kidney stones, weight loss
pearls: fluids; use outside of epilepsy (migraine prophylaxis, weight loss with Qsymia)

zonisamide (ZNS, Zonegran)
use: partial
pk: long half-life (qday dosing), no significant DI
toxicity: somnolence (excessive sleepy/drowsy), dizziness, kidney stones, weight loss
pearls: fluids; approved in Japan and Korea 1989; sulfonamide

levetiracetam (LEV, Keppra)
use: partial and generalized
pk: none; renal only
toxicity: somnolence, dizziness, behavioural changes (shorter fuse) esp higher doses
pearls: adjust for renal function, IV formulation, monitor mood

gabapentin (GBP, Neurontin)
use: partial
pk: absorption saturable, short half-life, no DI with AEDs
toxicity: fatigue, dizziness, ataxia
pearls: adjust for renal function; use outside epilepsy (pain postherpetic neuralgia, diabetic peripheral neuropathy; restless leg syndrome)

pregabalin (PGB, Lyrica)
use: partial
pk: none; renal only
toxicity: dizziness, ataxia, weight gain (not same as valproic acid; 5-10lbs)
pearls: adjust for renal function; use outside epilepsy (pain postherpetic neuralgia, neuropathic; fibromyalgia; [anxiety in EU])

phenobarbital (PB, generic)
use: partial and generalized
pk: inducer

toxicity: sedation, paradoxical hyperactivity, osteomalacia
pearls: better options available

benzodiazepines (diazepam, lorazepam, clonazepam, midazolam): acute (pulse) vs. long-term use; good for rescue meds, not for long-term

cannabidiol (CBD, Epidioloex): for severe forms of epilepsy (Lennox-Gastaut syndrome or Dravet syndrome, tuberous sclerosis); hard on GI (diarrhea)

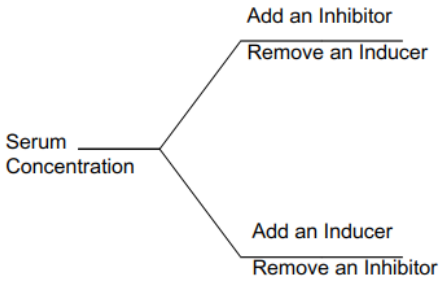
ethosuximide (ET, Zarontin)
use: generalized and absence*
pk: can be induced and inhibited
toxicity: sedation, GI (NV, pain)
pearls: DOC for absence seizures (younger patients)

Other AEDs (minor players and/or used for limited indications)
acetazolamide, brivaracetam, cenobamate, clobazam, eslicarbazepine, felbamate, perampanel, primidone, rufinamide, stiripentol, tiagabine, vigabatrin

1st-generation AEDs: PB PHT CBZ VPA FBM
- use in partial and primary generalized (exception CBZ not absence); vast clinical experience
- incomplete efficacy, unfavorable kinetics (saturation)
- narrow therapeutic window (small window between efficacy and toxicity), adverse CNS effects, drug interactions

2nd-generation AEDs: GBP LTG LEV ZNS TPM PGB TGB LCM CLB VGB OXC RUF PER BRV ESL
- safer, expensive (some generics), may help with intractable partial seizures
- not profoundly more potent; less drug interactions
- use outside of epilepsy

1st-generation influence metabolism
- inducers: phenobarbital, phenytoin, carbamazepine
- inhibitor: valproate



AED Impact on Hormone Kinetics
Decreased hormone concentration: phenobarb (primidone), phenytoin, carbamazepine, oxcarb^, felbamate, topiramate^, clobazam, perampanel, eslicarbazepine
- increased risk for OC failure and unplanned pregnancy - only with oxcarbazepine (>1200mg/d), topiramate (>200mg/d)

No impact on OCs (renal metabolism): gabapentin, lamotrigine (OCs induce lamotrigine), lacosamide, levetiracetam, pregabalin, tiagabine, valproate, zonisamide
Folic acid supplementation: essential for all women of childbearing potential for all AEDs

Desired outcomes: decrease seizure frequency and severity (seizure-free); minimize/avoid drug toxicities (weight gain/tremor); improve QoL (work, driving, child)
Common precipitating factors and reasons why patients might have increased seizure frequency: acute illness, sleep deprivation, increased stress, nonadherence

NEAD Study

What is the primary outcome of this study? Why did they even do it?
Background: Many women of childbearing potential take antiepileptic drugs, but the cognitive effects of fetal exposure are uncertain. We aimed to assess effects of commonly used antiepileptic drugs on cognitive outcomes in children up to 6 years of age.
- NEAD is the first study to show that fetal valproate exposure has dose-dependent associations with reduced cognitive abilities across many domains, show longitudinal changes in intelligence across ages 2–6 years, and show reduced right-handedness

What was found concerning studied medications? Carbamazepine? Lamotrigine? Valproate? Phenytoin?
- age-6 IQ was lower after exposure to valproate; children's IQ scores were related to maternal IQ scores in all exposure groups except for valproate
- high doses of valproate were negatively associated with IQ, verbal ability, non-verbal ability, memory, and executive function; other antiepileptic drugs were not
- children exposed to valproate did poorly on measures of verbal and memory abilities compared with those exposed to the other AEDs and on non-verbal and executive functions compared with lamotrigine (but not carbamazepine or phenytoin)

As a pharmacist, what recommendations can be gleaned from this article?
- mean IQs were higher in children exposed to periconceptional folate

Depression

Pathophysiology

Norepinephrine (NE)

role: attention and vigilance; learning and memory

location: synthesized primarily in neurons originating in the locus ceruleus (in brainstem; stained blue color); axons of these neurons project throughout the brain

synthesis: precursor tyrosine → L-DOPA (via tyrosine hydroxylase) → dopamine (via aromatic L-amino acid decarboxylase) → NE (via dopamine-β-hydroxylase)

termination of action: reuptake by NE transporters terminates action in synapse; transporters are primarily located in presynaptic terminal

receptors: alpha adrenergic, beta adrenergic (metabotropic=G-coupled protein →postsynaptic reactions: protein kinase activation, protein phosphorylation)

Serotonin (5-Hydroxytryptamine, 5-HT)

role: arousal, sleep-wake cycles, mood and motivation; modulate spinal cord sensory and motor neurons

location: synthesized primarily in neurons originating in raphe nuclei (brainstem); axons of these neurons project throughout the brain

synthesis: precursor tryptophan → 5-hydroxytryptophan (via tryptophan hydroxylase) → 5-HT (via aromatic L-amino acid decarboxylase)

termination of action: reuptake by serotonin transporters terminates action in synapse; transporters are primarily located in presynaptic terminal

receptors: 14+ kinds (all metabotropic except 1): activate different types of G proteins, thus different intracellular responses intiated; 5HT3 is ionotropic receptor

Signalling Mechanisms

NE receptors	α_1 ↑IP_3, DAG	α_2 ↓cAMP	$\beta_{1,2}$ ↑cAMP	
5-HT receptors	$5HT_{2A,B,C}$ ↑IP_3, DAG	5HT1A,B,D,E,F ↓cAMP	$5HT_{4,6,7}$ ↑cAMP	$5HT_3$ ligand-gated ion channel

note: α_2-adrenergic and $5HT_{1D}$ are presynaptic autoreceptors important for feedback inhibition; DAG = diacylglycerol, IP_3 = inositol 1,4,5-triphosphate, cAMP = cyclic AMP

Antidepressant action

The molecular targets of many antidepressants are known BUT the mechanism by which they produce an antidepressant effect is still unknown

Most antidepressant: block serotonin and/or norepinephrine uptake after initial exposure…

however: symptoms of depression are only alleviated after several weeks of treatment

antidepressant effect is caused by other changes in brain that are induced by blockade of reuptake

change in receptor sensitivity? neurotransmitter release? neurite outgrowth? neurogenesis?

Neurotransmitter systems implicated in depression

- reserpine induces depression in monkey; normal behavior resumed after paragyline (MAOI) and dopa

NE signaling: example of evidence: experiemental chemical (alpha-methyl-para-tyrosine; inhibits synthesis) catecholamine depletion in patients in remission from depression due to NE reuptake inhibitor experienced rapid relapse

5HT signaling: example of evidence: experimental dietary depletion of tryptophan (serotonin receptor) in patients in remission from depression due to SSRI treatment causes rapid relapse of depressive symptoms

- possible glutamate dysregulation in depression; recent interest in use of ketamine (NMDA receptor antagonist) in depression
- likely a complex interaction among many transmitter system.. and role for plasticity

Anxiety

Distinctive and overlapping symptoms of depression and anxiety

depression	**anxiety and depression**	**anxiety**
Depressed or hopeless	Irritability	Excessive worry
Loss of interest	Agitation/restlessness	Autonomic hyperactivity
Weight change	Concentration difficulties	Exaggerated startle response
Poor appetite	Insomnia	Muscle tension
Motor retardation	Fatigue	
Guilt/worthlessness		
Thoughts of death		

hippocampus encodes information into memories: appears to be smaller in people who have undergone severe stress; could explain PTSD, flashbacks, deficits in memory, fragmented memory for details of the traumatic event

amygdala processes incoming sensory signals and relays on to regions that interpret them: signal that a threat is present, trigger fear response/anxiety; role in storage of emotional memories

Antidepressants

Monoamine Oxidase Inhibitors (MAOI): Inhibits MAO (amines→deaminated); thereby increasing endogenous concentrations NE E DA 5HT tyramine
ADE: OH, CNS stimulation, wt gain
MAOI-food interactions: →can lead to hypertensive crisis (even brain hemorrhage)
- tryamine-containing foods: cheeses, wines, beer, chicken, sausage, etc.
- drugs containing sympathomimetic amines:
  - drugs that increase NE: L-DOPA, dopamine
  - drugs that block NE uptake: TCA, SNRI, etc.
  - drugs that increase NE release: decongestants, ephedrine, PSE, phenylpropanolamine

Possible interaction with drugs that increase 5HT (excess synaptic serotonin → serotonin syndrome): TCA, SSRI, SNRI, etc

in presence of MAOI:
- decreased neuronal MAO activity = ↑ NE concentration at nerve terminal
- decreased hepatic MAO activity = dietary tyramine enters circulation, gets to nerve terminal triggers NE release = vasoconstriction and cardiac stimulation

Tricyclic Antidepressants (TCA): Inhibits NE and/or 5HT transporters NET/SERT, thereby increasing NE and/or 5HT; also affect AChM, α_1, H_1
ADE:
Muscarinic ACh inhibition: dry mouth, blurred vision, constipation, urinary retention
α1 receptor inhibition: orthostatic hypotension (OH)
H1 recetpor inhibition: sedation (drowsiness), weight gain
acute toxicities: lower seizure threshold; arrythmias (sudden cardiac death); QT prolongation (affect Na channels in quinidine-like manner); lethal in overdose
TCA should not be combined with MAOI: increase NE via MAOI and increased release whereas TCA block reuptake
- combination potential very large increase in NE synapse: risk of hypertensive crisis

SSRI/SNRI
advantages
- fewer off-target effects: less sedation (some can produce), less weight gain; less cardiac toxicity (except citalopram QT), less effect on HR/BP

ADEs:
CNS stimulation induced by SSRI/SNRI
- initial nervousness, anxiety, restlessness, insominia
  - 5HT activation of 5HT receptors in hippocampus and limbic areas = axiety and insomnia
  - eventually anxiolytic effect
- dizziness possible
- sexual dysfunction

GI effects: NVD
- 5HT3 receptors in GI tract and area postrema ('chemoreceptor trigger zone')
- 5HT4 receptors in GI tract

Serotonin Syndrome: excess extracellular 5HT levels = accumulation of serotonin at 5HT receptors = toxicity
- alterations in neuromuscular activity: ataxia, myoclonus
- alterations in cognition: disorientation, confusion, hypomanis
- alterations in behavior: agitation, restlessness
- alterations in autonomic nervous system: flu-like symptoms fever, chills, sweating, diarrhea; cardiac: hypertension, tachycardia

treatment: supportive; sedation (benzos); cyproheptadine (nonselective serotonin antagonist)
Withdrawl from SSRI/SNRI; brain adapts to antidepressant therapy and
- flu-like symptoms (nausea, bone/muscle pain, fatigue, diarrhea); headache
- lightheadedness, dizziness
- uneasiness, restlessness
- sleep and sensory disturbances

mirtazapine
- alpha2-adrenergic receptors are presynaptic inhibitory autoreceptors (NE binds to = reduces release of NE via feedback)
  - mirtazapine inhibits these inhibitory receptors = increase firing rate of noradrenergic neurons and increase neurotransmitter release (therapeutic effect?)
- 5HT2A and 5HT3 serotonin antagonist

Theories on Mechanism of Action

Delayed effect of antidepressant effect of drugs:

1. Alterations of presynaptic autoreceptors or transporters and neurotransmitter synthesis

A. before treatment, neurotransmitters are released at pathologically low levels and exert steady-state levels of autoinhibitory feedback. The net effect is a pathologically low baseline level of postsynaptic receptor activity (signaling).

B. Short-term use of antidepressants results in an increase release of neurotransmitter and/or increased duration of neurotransmitter action in the synaptic cleft. Both effects caused increased stimulation of inhibitory autoreceptors, with increased inhibition of neurotransmitter synthesis and increased inbhition of exocytosis. The net effect is to dampen the initial effect of the medication, and postsynaptic receptor activity remains at pretreatment levels.

"the transient release in neurotransmitter might transiently increase the autoreceptor inhibtion of synthesis and release."

C. Chronic use of antidepressants results in desensitization of the presynaptic autoreceptors. Thus, the inhibition of neurotransmitter synthesis and exocytosis is reduced. The net effect is enhanced postsynaptic receptor activity, leading to a therapeutic level of signaling and therapeutic response.

"neuron sensed an increased activation of autoreceptors, so it stops synthesizing autoreceptors; downregulation of receptors or reduce its expression."

2. Activation of neuronal 'repair' mechanisms

'Neurotrophic' hypothesis of depression:

stress leads to sustained elevation of glucocorticoids, increased glutamate levels ('excitotoxicity')

→ neuronal damage and dysfunction; reduction in expression of BDNF (brain derived neurotrophic factor which is a neuronal growth factor)

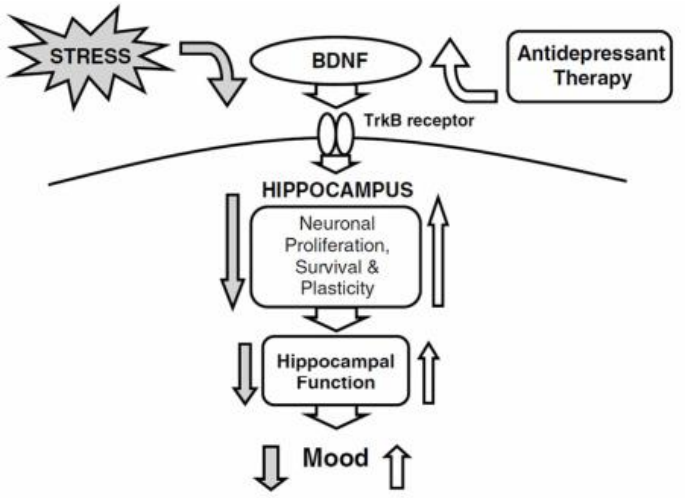
Effect of antidepressant therapy:

increase levels of transcription factor CREB which increases BDNF expression which enhances dendritic sprouting (opposite effect of stress)

- CREB: cAMP responsive element binding protein, where cAMP is a second messenger made in response to adenylyl cyclase activation

increase BDNF expression and prevents decrease in response to stress over time

upregulation of BDNF may slowly help 'repair' stress-induced damage that may contribute to symptoms of depression



Ketamine: NMDA receptor antagonist; also some agonism at opioid receptors; main use anesthetic; dissociative drug

- ketamine can induce rapid ADT effect which is relatively transient

Anxiolytics/Hypnotics

Benzodiazepines

–anxiety: alprazolam, lorazepam, clonazepam, diazepam, oxazepam (Serax), chlordiazepoxide (Librium), chlorazepate (Tranxene)
–insomnia: triazolam (Halcion), estazolam (ProSom), temazepam (Restoril), flurazepam (Dalmane), quazepam (Doral)
- bind to a regulatory site on GABA-A receptor; act allosterically to increase affinity of GABA for the receptor
  - GABA-A receptors mediate fast inhibitory synaptic response
  - electrical recordings of benzo treated neurons show increase in frequency of channel opening; no effect of benzos in absence of GABA
  - therefore, benzos reduce neuronal activation by enhancing inhibition

GABA-A receptors are chloride channels: Cl- negative ion influx into cell as activation leads to hyperpolarization = decreased firing
- pentameric (5 subunits): alpha (α), beta (β), gamma (γ) - thus, BZ and GABA don't bind to same site
  - **BZ** binding requires **α γ**
  - **GABA** binding requires **α β**

BZ as a group all have similar effects on GABA-A receptor pharmacology (ie. enhancing activation of GABA via Cl channel)
BZ differ from one another in PK properties: onset, duration of action, potency, active metabolites

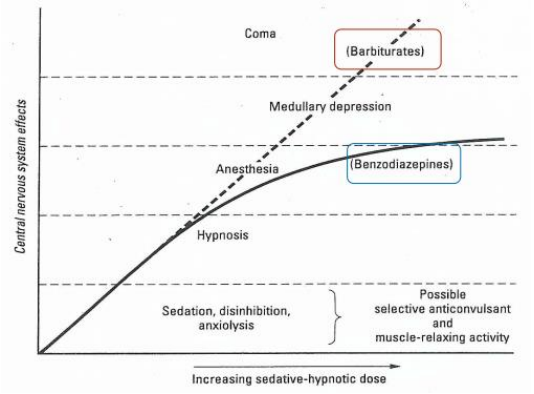
Insomnia

A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early. Alternatively, sleep that is chronically nonrestorative or poor in quality. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep. The impaired sleep produces deficits in daytime function

Goals: restore daytime functioning; avoid self-reinforcing pattern that may develop into chronic, long-term insomnia; hypnotic agents used combo with nonpharm

Ideal insomnia treatment: rapid absorption, rapid sleep induction, works through night, induces 'normal' sleep pattern, no residual effects, specific mechanism of action, safe in overdose, no rebound insomnia, no dependence, no tolerance, no ataxic effects, no intx alcohol/drugs, no respiratory depression, no memory effect

Benzos can provide symptomatic relief in insomnia and promote onset of sleep (decrease sleep latency)
but can disrupt 'normal' sleep pattern: decrease deep slow wave sleep (stage 3-4) and can decrease REM time; increase in stage 2 sleep time



Nonbenzos or Z-hypnotics – zaleplon (Sonata), zolpidem (Ambien), eszopiclone (Lunesta)
- bind to the BZ site on GABA-A receptor, but do not have benzo chemical structure
  - act preferentially at **α1 subunit**

α1 sedative effects of benzos **α2 anxiolytic** effects of benzos
GABA receptor heterogeneity: different subunits (6 α, 3 β, 3 γ)

flumazenil (Mazicon) is a benzodiazepine antagonist
- used clinically to reverse sedative action of benzos in acute overdose or during anesthesia

Barbiturates

- bind to GABA-A receptor, enhances action of GABA at low concentrations; can directly activate GABA receptors at higher conc (toxicity in OD); prolong duration of individual channel opening events; not commonly used as unsafe: death from respiratory and cardiovascular depression when overdose

Orexin Antagonists – suvorexant (Belsomra), lemborexant (Dayvigo)
- orexin (OX1 and OX2) receptors are metabotropic (G protein coupled); found in hypothalamus
- orexins A and B are peptide neurotransmitters implicated in wakefulness
- developed from finding that narcolepsy patients have loss of orexin neurons
- therefore they inhibit the wakefulness promoted by orexins, therefore promoting sleep

Circadian rhythms
- propensity to sleep is modulated by circadian rhythms controlled by suprachiasmatic nucleus (SCN) in hypothalamus
- primary pacemaker for neuroendocrine rhythms, temperature cycle, sleep-wake activity; jet-lag slow shifting of circadian rhythms to new light-dark cycle
- Melatonin synthesized in pineal gland (wt 150mg); pinealocytes specialized secretory cells; tryptophan is precurser; levels highest at night in absence of light
  - claims for use in insomnia and jet lag/adjustment of circadian clock in circadian sleep-wake rhythm disorders

Day: SCN firing inhibits melatonin synthesis Night: absence of SCN firing stimulates melatonin synthesis Light stimulates SCN firing, inhibit melatonin synthesis
- circadian clock: melatonin: clock timing, pituitary output, adrenal physiology, immune system, sleep onset

Melatonin Agonists – tasimelteon (Hetlioz), ramelteon (Rozerem)
- high affinity for MT1 and MT2 receptors: metabotropic (G protein coupled) involved in maintenance of circadian rhythm underlying normal sleep-wake cycle
- tasimelteon approved for 'non-24h sleep-wake rhythm disorder'
  - periods of insomnia and sleepiness when circadian pacemaker not entrained to a 24h light cycle (can occur in blind individuals)
- ramelteon is used for insomnia

Antihistamine
–diphenhydramine, doxylamine
- H1 histamine receptor antagonist
- feel sleepy, but do not improve sleep; long half-life (8-10hr)
- decreased alertness, daytime sedation, prolonged reaction times on day following use
- SE: dizziness, anticholinergic side effects, cause REM suppression and REM rebound when discontinued

Histamine is a neurotransmitter produced by tuberomammillary nucleus of posterior hypothalamus
- projections throughout brain and SC; firing rate of histaminergic neurons is correlated with states of arousal
  - fire fastest during wakefulness - fire slower during sleep

Antidepressants
- those with sedative side effects: amitriptyline, doxepin, trazodone; used in lower dose for insomnia than depression
- doxepin (Silenor): TCA low dose 5-10x lower than used for depression; FDA approved for insomnia characterized by sleep maintenance difficulty
- sleep effect probably mediated by H1 histamine receptor blockade

Functions of sleep: hypothesized to be important for enhancement of learning that happened during previous day AND/OR elimination of irrelevant memories
sleep, learning, memory:

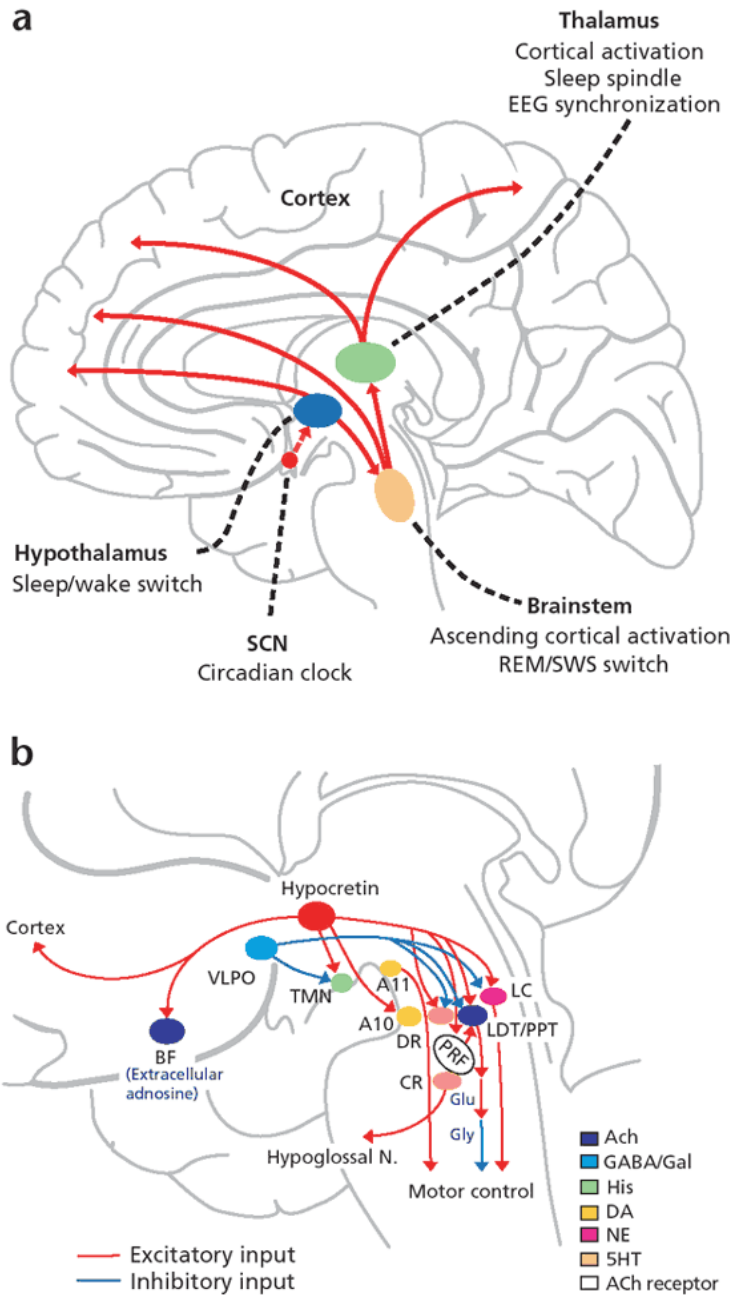


Figure 1: Hypothalamic and brainstem sleep/wake regulation systems, in relation to common sleep disorders and their pharmacological treatment. (**a**) Distinct roles of the brainstem, thalamus, hypothalamus and cortex for vigilance control. (**b**) Recent discoveries of the sleep-promoting GABAergic/galanininergic (Gal) neurons in the ventrolateral preoptic area (VLPO) and the wake-promoting hypocretin/orexin neurons in the lateral hypothalamus focus attention on the hypothalamus. Destruction of these systems induces insomnia and narcolepsy, respectively, mirroring the pioneering clinical observations during the encephalitis lethargica epidemic. Although no direct interaction between the two systems has been reported, both VLPO and hypocretin systems innervate the main components of the ascending arousal system, such as adrenergic locus coeruleus (LC), serotoninergic dorsal raphe (DR) and histaminergic tuberomammillary nucleus (TMN). The VLPO system inhibits, and the hypocretin system activates, these systems. Thus, the hypothalamus may serve as a center for the 'sleep switch' under the influence of the circadian clock. In addition to these ascending arousal systems, pharmacological evidence suggests the involvement of dopamine (DA), especially in the ventral tegmental area (A10), for the control of alertness. The DA system, including descending A11 projections, may also be particularly important for sleep-related motor control in conditions such as cataplexy and PLM. Recent anatomical and pharmacological evidence suggests that serotonin (5HT) is important for the motor control of the hypoglossal nucleus, and dysregulation of this system may be involved in upper airway resistance in obstructive sleep apnea. Histamine (His) is a wake-promoting amine, but it has a variety of peripheral actions. Histaminergic compounds are not widely used in sleep medicine, except the CNS-permeable H1 antagonists for a small number of insomnia patients. Benzodiazepines (BZs) act on the $GABA_A$/BZ-Cl^- macromolecular complex, and may act on any part of the arousal system shown here. BF, basal forebrain cholinergic nuclei; LDT/PPT, laterodorsal tegmental nuclei/pedunculopontine tegmental nuclei; CR, caudal raphe; PRF, pontine reticular formation; ACh, acetylcholine; PLM, periodic leg movements during sleep; NE, norepinephrine; GLY, glycine; GLU, glutamate.

Depression
• Utilize patient-specific information to select an appropriate antidepressant
• Identify the mechanism of action, common side effects and monitoring for antidepressants

- For select antidepressants, explain why each medication would be preferred or avoided based on its pharmacologic profile
- Explain the importance of the STAR*D trial and how the outcomes have impacted clinical practice
- Create an appropriate treatment and monitoring plan for a patient initiated on an antidepressant

Depression Mnemonic – **SIG: E CAPS** 5+ of the following (nearly every day) over a 2-week period with at least one depressed mood or lost interest/pleasure
Sleep changes (increase or decrease)
Interest (loss) and/or low moods
Guilt (worthlessness)
Energy (loss)
Cognitive or concentration difficulties
Appetite and/or weight change
Psychomotor agitation (anxiety) or retardation (talking slowly)
Suicidal ideation, plan or suicide attempt

Patient Health Questionnaire (PHQ-9): to screen and monitor depressive symptoms; self-admin by pt, scored by provider; score of 0-3 based on freq of symptom
0-4 none or minimal symptom severity 5-9 mild 10-14 moderate 15-19 moderate-severe >20 severe
*as score increases, symptom severity increases Q#9 thoughts that would be better off dead or of hurting yourself in some way (suicide screen)

Antidepressants

- The first-line treatments for depression are antidepressants
- SSRIs, SNRIs, bupropion and mirtazapine are first-line
- Antidepressants are believed to be equally effective; some are better tolerated
- Antidepressants should be titrated to therapeutic doses

citalopram	20-40mg qday max 20mg for hepatic, >60yo, PM or concomitant 2C19 inhib	dose-dependent QTc-prolongation; monitor EKG avoid in patients with known QTc prol or on other prolonging agents inexpensive (<$5/mo)
escitalopram	10-20mg qday max 10mg: hepatic, geriatric	similar but less concern with QTc-prolongation (Lexicomp amio-citalopram X; amio-escitalopram D)
fluoxetine	20-80mg dose adj hepatic/2D6 inhibitor	--unique: potential for weight loss may be more stimulating compared to other SSRIs; don't take at bedtime longest HL with active metabolite; desirable for pt with poor adherence self-tapers at discontinuation, requires longer washout period when starting MAOI (5wk)
fluvoxamine		not approved for or routinely used for depression; approved for OCD; 1A2 inhibitor
paroxetine	20-50mg qday (IR) dose adj hepatic/renal/2D6 inh	--unique: anticholinergic, antihistamine (sedation, dryness, constipation, delirium, etc.) avoid in older pt due to high antichol; higher incidence of weight gain; AEs limit the utility discontinuation syndrome more pronounced (short HL); pregnancy category D
sertraline	50-200mg qday dose adj hepatic	--unique: diarrhea; large dosing range may be desirable safe in MI and CHF; often preferred in pt with cardiac history usually preferred in pregnancy, breastfeeding, geriatric?
duloxetine	30-120mg daily dose adj hepatic/renal	also for musculoskeletal, neuropathy, fibromyalgia certain doses may require prior auth
venlafaxine	75-225mg daily (XR) dose adj hepatic/renal	inhibits primarily SERT at <150mg; similar to SSRI pronounced discontinuation syndrome; available IR form requires bid-tid dosing (GI bypass, tube feeds)
desvenlafaxine	50-100mg qday dose adj hepatic/renal	active metabolite of venlafaxine; less BP increase vs. venla only approved to treat MDD; generic still expensive
levomilnacipran	40-120mg daily dose adj renal/3A4 inh	only approved for MDD brand name only, limited clinical use, may require prior auth
bupropion	150-450mg daily (XR) 150-200mg bid (SR) avoid severe hepatic/renal	--unique: overall "activating": headache, HR BP, insomnia, tremor, anxiety/agitation (on edge), appetite, wt loss; CI: seizures/eating disorders; decrease seizure threshold; not associated with sexual dysfunction dose in morning and early afternoon (close to bedtime could impair sleep) often adjunct to SSRI/SNRI; not rec'd in anxiety or PTSD; also approved for smoking cessation (Zyban) and obesity (Contrave in combo with naltrexone)
mirtazapine	15-45mg dose adj hepatic/renal	--unique: overall "sedating": increase appetite, wt gain, sedation, orthostasis; anticholinergic effects; doses >15mg less sedating; not associated with sexual dysfunction often adjunct to SSRI/SNRI
amitriptyline	100-300mg daily	rarely used in practice (for depression) d/t SE profile and safety concerns (OD is lethal); avoid suicide idea often used for sedating effects and/or pain management nortriptyline less associated with anticholinergic, sedating, orthostatic effects than amitriptyline monitor EKG and electrolytes
nortriptyline	50-150mg daily	
selegeline	6-12mg/24hr patch	rarely used in practice to SE profile and safety concerns; patch more comman than oral MAOIs requires washout period; cannot be combined with other ADTs 6mg patch does not require tyramine restriction; patch allows unique ADT delivery method; expensive
trazodone	50-200mg tid	rarely used for ADT effects; primarily used at low doses 50-100mg for sleep, due to H1 properties orthostatic hypotension (alpha1); does not cause sexual SEs but may cause priapism
vilazodone	20-40mg daily	similar side effects to SSRIs brand names costly role in treatment less defined
vortioxetine	10-20mg daily avoid severe hepatic	

SSRI
MOA: Block the reuptake of serotonin (5HT) from synapse via actions on serotonin transporter (SERT) → increases [5HT] in the synapse
Common side effects: GI upset, headache, drowsiness, appetite increase or decrease, *sexual dysfunction; should improve: irritability and restlessness
Monitoring: Tolerability, side effects, symptom reduction, EKG and electrolytes, suicidal ideation
Discontinuation Syndrome
- May occur if abruptly stopping an SSRI, particularly after long periods of use
- Symptoms may include: headache, GI upset, flu-like symptoms, sleep disturbances, mood disturbances, irritability and sensory disturbances ("brain zaps")
- More likely to occur with short t1/2 drugs (paroxetine)
- Antidepressants should be tapered to avoid this!
Cost: <$10
when to consider: first-line, treatment-naïve patients, low cost, anxiety disorders
when to avoid: citalopram (escitalopram) in QTc prolongation; paroxetine: overweight, geriatric, pregnancy

SNRI
MOA: Block the reuptake of 5HT and norepinephrine (NE) from synapse via actions on SERT and norepinephrine transporter (NET) → increases [5HT] and [NE] in the synapse
Common side effects: Serotonergic effects (see SSRIs), increase in HR and BP, insomnia, agitation, anxiety
Monitoring: Tolerability, side effects, symptom reduction, EKG and electrolytes, renal and hepatic function, BP
Discontinuation Syndrome: Similar to SSRIs; most common with venlafaxine
Cost: more expensive than SSRI
when to consider: first-line, neuropathic pain, less sedation with SSRIs
when to avoid: uncontrolled HTN, cost concerns; duloxetine: hepatic disease; desvenlafaxine/levomilnacipram (limited insurance coverage)

NDRI – bupropion
MOA: Block the reuptake of NE and dopamine (DA) from synapse → increases [NE] and [DA] in the synapse
Common side effects: Headache, increase in HR and BP, insomnia, tremor, agitation, anxiety (activating effects), decreased appetite, weight loss
Contraindications: Current or h/o eating disorders (electrolyte abnormalities = increased seizures) or seizure disorder (decrease seizure threshold)
Monitoring: Tolerability, side effects, symptom reduction, EKG and electrolytes, BP, appetite and weight, seizures
Cost: More expensive than SSRIs, but all forms are generic
when to consider: adjunct therapy; experienced sexual dysfunction with SSRI/SNRI; concomitant smoking, low energy
when to avoid: seziures, eating disorders, alcohol abuse

Atypical – mirtazapine
MOA: Presynaptic alpha-2 antagonist → increased NE and 5HT transmission; Antagonist at 5HT2 and 5HT3, M1, H1 and alpha-1 receptors → side effects
Common side effects: Weight gain, increase in appetite, sedation, anticholinergic effects, orthostasis
Monitoring: Tolerability, side effects, symptom reduction, EKG and electrolytes, appetite and weight, sedation, BP
Cost: More expensive than SSRIs
when to consider: adjunct therapy; experienced sexual dysfunction with SSRI/SNRI; poor appetite, insomnia
when to avoid: overweight, metabolic concerns

TCA
MOA: Block the reuptake of 5HT and NE from synapse via actions on SERT and NET → increased [5HT] and [NE] in the synapse; Antagonist at cholinergic (M1), histaminic (H1) and alpha-1 receptors → side effect profile
Common side effects: Anticholinergic effects, confusion, delirium, orthostasis, weight gain, sedation, sexual side effects
Contraindications: Recent MI Precautions: Cardiotoxicity and lethality in overdose, decrease seizure threshold
Monitoring: Tolerability, side effects, symptom reduction, EKG and electrolytes, BP, appetite and weight gain, seizures
Cost: Inexpensive, often <$10

MAOI
MOA: Block enzyme monoamine oxidase (MAO) that is responsible for metabolizing 5HT, NE and DA → increased synaptic [5HT], [NE], and [DA]; Those available in US are irreversible inhibitors; need to synthesize new enzyme to reverse the effects
Common side effects (vary by agent): Anticholinergic effects, weight gain or loss, sexual dysfunction, elevation in LFTs, orthostasis, insomnia
Contraindications: Concomitant use of medications that increase [5HT], [NE], and/or [DA]; E.g. Antidepressants, amphetamines, triptans, methylphenidate, levodopa, dextromethorphan
Precautions: Liver impairment, cardiovascular history, cerebrovascular history
Monitoring: Tolerability, side effects, symptom reduction, EKG and electrolytes, BP, appetite and weight changes, seizures, diet
Cost: Expensive, limited availability
Required Washout period: Wait 4-5 x t1/2 of ADT or contraindicated mediations before starting an MAO-I; Wait 14 days after stopping MAO-I to start another ADT
Dietary restrictions: Tyramine containing foods can lead to hypertensive crisis; E.g. Cheese, overripe fruit, sausage, salami, red wine, fermented products, etc.

Augmentation agents: antipsychotics (aripiprazole, brexpiprazole, olanzapine, quetiapine, risperidone, ziprasidone); buspirone, lithium, liothyronine (T3), ketamine, esketamine

Esketamine Nasal Spray (Spravato)
- FDA approved indications: Treatment resistant depression + an oral antidepressant; Major depressive disorder with suicidality
- MOA: NMDA receptor antagonist, ?mechanism for antidepressant effects
- Common side effects: elevated blood pressure, CNS changes (dissociation, dizziness, sedation, etc.), nausea, vomiting
- Cost and Availability: Only available through REMS approved pharmacy, facility and patient; Must be administered on site under monitoring

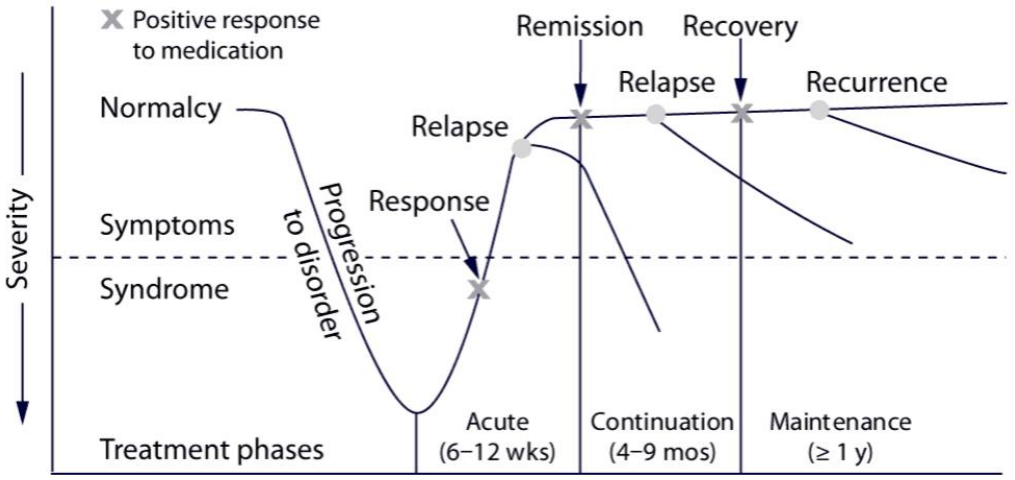
Treatment Implementation

Initate low dose, titrate slowly; provide info on expectations in terms of symptom response:
Week 1: anxiety, appetite, sleep
Week 2-3: motivation, concentration, memory
Week 4-6: low moods, hopelessness, loss of interest, sleep
Week 6-12: full benefit at treatment dose

Monitor adherence, tolerability of side effects
Labs: BMP (renal, electrolytes, sodium); LFT (hepatic), TSH, VitD, iron panel (if low at baseline), EKG (QTc prolong)
Efficacy: goal is remission: minimal symptoms or return to baseline; undesirable outcomes may include nonresponse, partial response, relapse or recurrence

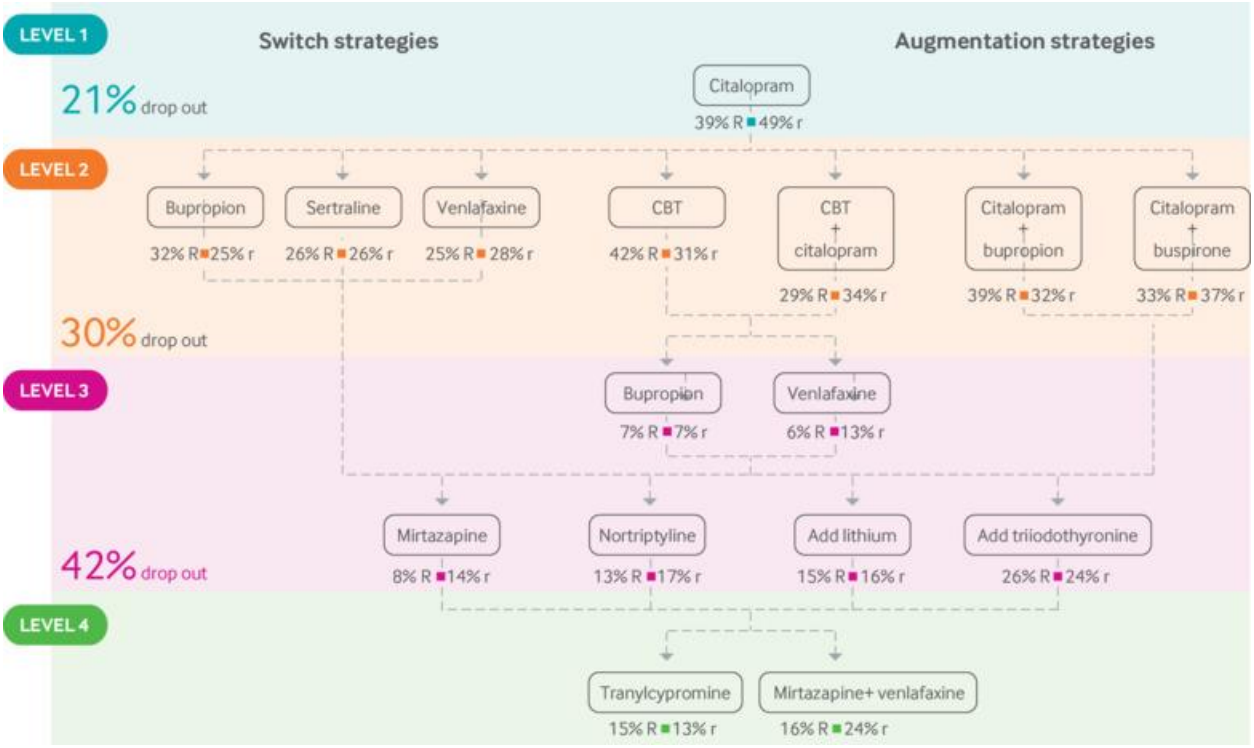
Outcome 1: Remission
- move into continuation phase
- continue current ADT and dose
- assess tolerability, adherence

Outcome 2: Relapse (inadequate response)
- evaluate adherence
- rule out other causes for nonresponse
- adjust the medication regimen



STAR*D Trial
primary: **Remission (%R)**, based on Ham-D/QIDS score
secondary: **Response (%r)**, defined as >50% decrease in QIDS score

Cumulative Remission Rates Level 1: 37% Level 2: 57% Level 3: 63% Level 4: 67%



STAR*D Trial Summary
- The goal of treatment should always be remission
- The odds of achieving remission decrease with each additional step
- Pharmacological differences do not necessarily equate with clinical differences
  - No antidepressant was not significantly more effective than another
- Switching or combining antidepressants are both reasonable options
  - Patients may respond to a different medication in the same class
- MAO-Is, TCAs and lithium are less well-tolerated than other antidepressants

Simplified Treatment Algorithm
optimize ADT: SSRI, SNRI, bupropion, mirtazapine
switch alternative ADT: same class or another class
add ADT with different mechanism: bupropion, mirtazapine
add non-ADT agent: atypical antipsychotic, T3, lithium
switch ADT with less tolerable SE profile: TCA, MAOI

Special Populations

Geriatric

- Depression may manifest differently, with more somatic symptoms and fatigue
- Avoid anticholinergic medications or those with cardiac effects when possible (Paroxetine, TCAs)
- Initiate at lower doses and titrate more slowly

Pregnant

- Psychotherapy is first line for mild-to-moderate depression
- Both antidepressants and untreated depression may be associated with complications
- Therefore, must weigh risks vs. benefits of antidepressant treatment
  - Key Question: If left untreated, could the mother's depression result in harm to the mother or baby?
- SSRIs are most commonly used (and studied), with the exception of paroxetine (Category D; septal heart defects)

Pediatric and Adolescent

- SSRIs are first-line for depression in children and adolescents
- SNRIs, mirtazapine and bupropion may be appropriate if treatment resistant
- Start with initial lower doses and titrate to effect
- Monitor frequently, due to potential for increase in suicidality (BBW)
- Monitor closely for hypomania or mania

Ceutics

SSRI have nonlinear kinetics, gender differences, age dependency, clinically relevant drug-drug interactions
- nonlinear PK due to
  1) low capacity but high affinity process (2D6)
  2) high capacity but low affinity process

2D6 and SSRI normal function (2D6 *1 *2) decreased function (*9 *10 *41) no function (*3 *4 *5 *6) deletions (*5) multiplication denoted by xN

	activity (%pt)	genotypes	implication	therapeutic recommendation
UM	>2.0 1-2%	duplications of functional alleles	increased metabolism to less active; lower plasma conc = failure	select alternative drug not metabolized by 2D6
EM	1-2 77-92%	two normal function or two decreased or one normal/one no function or one normal/one decreased function	normal metabolism	initiate therapy with recommended starting dose
IM	0.5 2-11%	one decreased function and one no function	slightly reduced metabolism; higher plasma conc more = SE	initiate therapy with recommended starting dose
PM	0 5-10%	only no functional	greatly reduced metabolism; higher plasma conc = SE	select alternative drug, or paroxetine reduction 50% of starting dose and titrate to response

2C19 and SSRI increased function (2C19 *17) no function (2C19 *2 *3)
same thing as above

Paroxetine
- most potent SSRI, but lowest selectivity; also blocks muscarinic receptors (anticholinergic effects only at toxic doses); pure enantiomer, PK uniform vs. fluoxetine
- first-pass is saturable resulting in nonlinear PK and variable HL: after 15 days of 20mg/d, HL ↑12%, AUC ↑191 to 1481ng/hr/ml; F higher after several doses
- 2D6 polymorphisms exist; nonlinear PK due to low capacity but high affinity process; ex. tamoxifen 2D6 substrate, to get active; won't have efficacy if inhibited
- paroxetine most potent inhibitor of 2D6 among SSRI; exclusively inhibits 2D6; inhibition lasts 3-7 days which is easier to handle compared to fluoxetine

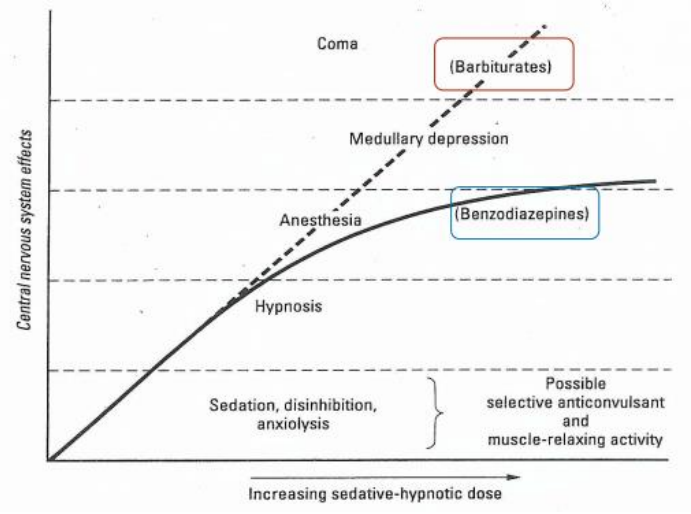
Fluoxetine
- racemic mixture; S- 1.5x more potent; metabolite of S- 20x more potent
- first-pass metabolism makes F <90%; lipophilic with large Vd (sequestration in lysosomal compartment); accum in brain is less than other SSRI
- nonlinear metabolism: F increases with dose; liver impairment reduces clearance
- 2D6 is key in R- and S- fluoxetine and S-norfluoxetine, but not R-norfluoxetine; although 2D6 involved, paroxetine does not affect fluoxetine metabolism
- HL fluoxetine 1-4 days; norfluoxetine 7-15 days; steady state achieved at 1-2.2 months
- interactions due to inhibitory effects: 3A4 with carbamazepine, alprazolam; 2C9 with phenytoin; 2D6: TCAs and neuroleptics
- the long half life of fluoxetine requires therapeutic drug monitoring (TDM) to safely switch to another antidepressant as it can affect metabolism weeks after dc'd

Sertraline
- second most potent SSRI; binds to dopamine transporters and can block α1; contains two chiral centers but only one enantiomer contained in formulation
- slow but complete absorption from GI; Vd >20L/kg suggesting extensive binding in tissues;
- linear PK elimination rate is constant and is higher in young men (30% faster) than females or those >65yo
- HL 26 hours; N-desmethylsertraline more slowly eliminated (60-100hrs), only 10% of potency
- PK interactions minimal; can inhibit 3A4 influencing concentration of clozapine which can increase upon sertraline dc'd; can interact with phenytoin 2C9

Citalopram
- most selective SSRI for SERT>NET; racemic but main effects due to S- main metabolite (N-desmethylcitalopram); some α1 H1 activity; first-pass minor (F 80%)
- biphasic elimination (HL 36hrs, metabolite 72-96hrs); linear relationship between dose and plasma conc; clearance is significantly reduced in elderly
- 2D6 and 2C19 involved in metabolism; ppl taking carbamazepine have increased clearance of citalopram which supports role for 3A4 metabolism
- UM consider alternative drug not metabolized by 2C19; PM consider 50% dose reduction of starting and titrate to response

MAOI are generally nonselective and irreversible (suicide inhibitor); >2weeks required for MAO activity to recover
MAO-A degradation of 5HT NE tyramine = necessary one for treating depression; predominates in GI and liver;
  - inhibition upon beer, wine, cheese, soy, etc; accum of tyramine at adrenergic nerves and secretory vesicles induces E and NE release and increase BP
MAO-B degradation of dopamine

Selegiline
- irreversible MAOI, inhibits MAO-B > MAO-A
- high doses effective for depression treatment; but would lead to potential tyramine provoked events (30-60mg/day)
- transdermal patch overcomes dietary restrictions and can provide continuous release of selegiline
- 2B6 2C9 3A4 metabolism; interactions with risperidone alprazolam (inhibition of their degradation); carbamazepine causes two-fold increase of selegiline conc.



Barbiturates – linear response
- reversibly depress activity of all excitable tissues
- CNS extremely sensitive, but high doses effect CV/resp
- promote binding of GABA to GABA-A receptor and binding of benzos
  - prolong the GABA-A channel opening
- induce all degrees of depression from mild sedation to general anesthesia
- tolerance can occur: functional (PD): confers cross-tolerance or PK
- metabolized by liver; acutely inhibit biotransormation of drugs = DDIs
- chronically induce 1A2 2C9 2C19 3A4
  - accelerate vit K/D metab, steroid horm, OCs; form toxic metabolites
- still indicated for emergency seizure, presurgical sedation (parenterally)

Benzodiazepines – plateau response
- promote binding of GABA to GABA-A receptors (positive allosteric regulator)
- benzos bind at alpha gamma subunit interface; α 1 2 3 5 high affinity for benzos, not 4 6
  - α1 sedation effect and amnesia; cortex, thalamus, cerebellum; 60% of GABA-A receptors
  - α2 anxiolytic and muscle relaxant effect; limbic system, motor neurons, dorsal horn of SC
- difference in affinity may reflect PD properties of benzos

Potency
- low-medium: chlordiazepoxide, oxazepam, temazepam: effectiveness and low toxicity make them first line for insomnia and anxiety
- high: alprazolam, lorazepam, clonazepam: can be used for panic disorder, OCD, mania, agitation; higher potency = higher risk of undesired effects, consider PK

Benzo PK
- well absorbed by GI, quickly distribute to CNS
- classified in terms of elimination HL: short (1-12hr), intermediate (12-40hr), long acting (40-240hr); remember ~5 HL necessary to eliminate drug from body
- extensively metabolized by 3A4 2C19; three major stages characterize metabolism:
  1. removal of substituent in R1 or R2 on diazepine ring, which results in biological active cpd
  2. hydroxylation at C3 also yield active derivate
  3. conjugation with glucuronic acid (HL 6-12hr)
- benzos do not significantly induce synthesis of their CYPs; however OC, abx, cimetidine inhibit their metabolism

alprazolam: short acting, high potency; anxiety and panic disorders; rebound anxiety can occur with abrupt dc given short elimination HL
clonazepam: short acting, high potency, also acts as serotonin agonist; effective in mania; given low solubility less likely to cause anterograde amnesia
lorazepam: short acting, high potency; anticonvulsant and mania; goes directly to glucuronidation w/o previous CYP metabolism; *DOC renal/hepatic impair
diazepam: long acting, medium potency; anticonvulsant, sedation, anxiolysis, muscle relax; IV IM PO PR
  low doses anxiolytic due to α2 GABA-A recptor medium doses myorelaxation due to α2 in spinal cord and α3 high doses sedation amnesia α1
  - unique: generates three active metabolites (oxazepam, temazepam, desmethyldiazepam/nordazepam); reason for long HL
  - HL increases ~1hr for each year >40yo; consider build up which can induce side effects of oversedation, anterograde amnesia
midazolam: short acting, more potent than diazepam; also interferes with GABA uptake; used preop anxiolytic and sedation;
  - parenteral prep has acid pH makes it water soluble: no propylene glycol required, less painful injections
  - amnestic effects desired; more intense than diazepam but shorter than lorazepam

ADE
- age related pathophys changes: increased sensitivity in elder due to accum of metabolites
- CNS: sedation, drowsiness, motor impairment, ataxia; anterograde amnesia; disinhibition (behave out of character); delirium; combo other CNS dep very toxic
- paradoxical effects: rare but can occur in recreational, children, high-dose: violence, irritability, suicidal behavior

Z-compounds: selectivity for α1 used for sedation/insomnia; tolerance and physical dependence still expected
zolpidem: shortens sleep latency and prolongs total sleep; approved for short-term insomnia; large overdoses do not produce severe respiratory depression

Anxiety

1. Identify symptoms of anxiety 2. Recognize causes of these disorders and other medical conditions with similar symptoms 3. Differentiate between disorders
4. Classify treatment options for these disorders 5. Create an appropriate treatment plan for a patient with one of these disorders

Background
Fear: normal emotional response to stressor/threat; fight/flight, duration appropriate, sx can be severe; doesn't require phm
Anxiety Disorder: anticipation of a future threat, excessive duration/intensity; commonly occur w/o precipitant; interferes with life; pervasive, pronounced, distressing; longer duration

Physical symptoms: abdominal pain, palpitations, tachycardia, sweating, flushing, SOB, muscle tension, headache, fatigue, tremor, chest pain

Drug-induced: stims, carbamazepine, pheny, bupropion, SSRI/SNRI, steroids, dopa agonists, albuterol, pseudoeph, levothy, etc

Anxiety Differential
similar presentation: arrythmias, angina, HTN, MI, hypothyroid, hypoglyc, drug-induced anxiety, neurological, psych, substance misuse
labs: CBC, chemistry, TSH, UA, ECG, toxicology

Common comorbidities: MDD (61-82%), other anxiety disorder (22-34%), agoraphobia (20-25%), substance/drug/alcohol (27-33%)

GAD-7 mild GAD 5-9 mod GAD 10-14 severe GAD >15
Hamilton Anxiety Scale (HAM-A): not self-administered; needs trainer; good for clinical trials (gold standard)
decreases >50% successful treatment response; score <7 patient in remission

Panic Attack: abrupt surge of intense fear or discomfort; reaches peak within minutes
- have at least 4/13 physical symtoms in DSM-5 criteria
Panic Disorder: recurrent, unexpected panic attacks with at least 1+ month persistant worry/concern and/or significant maladaptive changes in behavior

Acute stress disorder: sx that last >3days and <1mo; intrustion, negative mood, dissociative, avoidance (avoid memory/thoughts/ppl), arousal sx (sleep/irritable)
PTSD: symptoms that persist >1 month and cause significant/impairment in functioning; avoidance, negative mood, arousal symptoms

Goals: remission (complete resolution of somatic and psychiatric symptoms); resolve/minimize functional impairment, improve QoL, prevent relapse, pt-specific
Panic disorder: decrease frequency of panic attacks, no/minimal anticipatory anxiety, no agoraphobic avoidance
SAD: reduce physiologic symptoms (voice shaking, tachycardia, sweating), decrease phobic avoidance
PTSD: reduce severity of core symptoms, restore psychological sense and trust; limit generalization of danger experienced, restore normal development

Nonpharm
Cognitive Behavioral Therapy (CBT) 1st line: combo with pharm therapy better than either alone
others: eyemovement desensitization and reprocessing; exposure therapy, supportive therapy (meditation, breathing, mindful, exercise), barriers

SSRI/SNRI 1st line for all anxiety disorders; class effect
Onset of action: 2-4 weeks to see effect; 6-12 weeks to see full improvement start at low dose, can increase in first 1-2 weeks; see dosing chart
ADEs: headache nausea (slow titration of dose, HS dosing, take with food), sleep disturbances (sleep hygiene, AM vs. PM), sexual dysfunction (reduce dose, once weekly one-day holiday, add bupropion)
Discontinuation symptoms: taper over few weeks to months

Benzos most effective class for relief of acute anxiety symptoms; relieve somatic and autonomic symptoms but not cognitive symptoms; relapse rates higher
select based on PK - all equally effective; onset of action (proportional to lipid solubility), half-life (longer preferred in anxiety disorders)
metabolism: avoid hepatic oxidation in liver disease and elderly LOT (lorazepam, oxazepam, tempazepam) don't have active metabolites
misuse potential: risk factors high doses, potent/short-acting, long duration of therapy; minimize using adequate dosing intervals, avoid prn, short-term use
Place in therapy: symptomatic relief during delay to effect with ADT; short-term distress (air travel, procedures); rarely used long-term for refractory anxiety
- less effective than ADTs; relapse rates higher than ADTs; work quicker than ADTs; limit use to 2-4wk
Avoid benzos: elderly, hepatic impair, concurrent opioid use, concurrent use of other CNS depressants (incl alcohol); past/present substance misuse
Dosing: start low (relieve anxiety and minimize ADE); titrate dose weekly if needed; decide scheduled vs. prn
Benefits stopping benzo: improved memory/cognition, decreased motor vehicle risk; decreased risk of hip fractures
Withdrawal: seizures can be life-threatening with risk factors being high doses, long durations of threapy, other drugs lowering seizure threshold, seizure disorder
seizures can occur within 3 days of short-acting benzos and 7 days long-acting benzos
symptoms: psychological (rebound anxiety, jitter, insomnia, paranoia, memory); physical (diaphoresis, malaise, headache, muscle tension, tremor, nausea, etc)
Tapering: consider starting/titrating first-line anxiety med or CBT (CBT superior dc outcomes); adjunct pregabalin useful
- slow taper (mo-yrs); switch to long-term benzos and those with active metabolites; consider available strengths
- as the dose gets smaller the size of each dose reduction should decrease; try never to go backwards (incr dose); may still experience withdrawal sx
- tapering resourcs: PharmacistLetter Benzo Toolbox; Ashton Manual, Boswick JR et al current psychiatry 2012; Lader M et al CNS drugs 2009

TCA 2nd line for anxiety disorders except SAD; effective as SSRI but more ADEs; class effect but imimpramine/clomi studied; start low titrate; avoid in suicide risk
buspirone 2nd-line or augmentation (long-term efficacy inconsistent) does not improve mood/treat depression; partial 5HT1A presynaptic partial agonist
BID-TID dosing; started at 10-15mg/day in 2-3 divided doses; titrated by 5mg/day increments every 2-3 days; usually dose 20-60mg/day
Onset: max effect 4-6 weeks; should not be used prn ADE: dizziness, nausea, headache benzos use in last month resulted in decreased efficacy
hydroxyzine 2nd-line or augmentation; ADE anticholinergic; lack of cormobid benefit; efficacy used 4+ months not well studied; initial 25mg bid, max 400mg/day
pregabalin 2nd-line or augmentation; used in 150-600mg/day (>300mg meh?); immediate onset similar to benzos; improved outcomes when used with SSRI/SNRI
atypical antipsychotics 2nd-line or augmentation; lower doses than used in other disorders; onset 1-2 weeks - aripipr, olanz, quetiap, risperid, ziprasidone studied

others: - MAOI 3rd-line d/t ADE/dietary restr - mirtazapine - vilazodone/vortioxetine - anticonvulsants

GAD Treatment Summary
1st line: SSRI, SNRI 2nd-line: TCA, pregabalin, benzos, buspirone, atypical antipsychotics, hydroxyzine, mirtazapine, anticonvulsants last-line: MAOI

Panic Disorder Treatment Pearls
Benzos can be used monotherapy (if no underlying mood issues; commonly used adjunctive therapy); - aerobic exercise can prevent attack; avoid substances
PD with agoraphobia: psychotherapy (CBT) + pharm necessary
PD w/o agoraphobia: CBT or pharm alone effective
Not effective: buspirone, antihistamines, antipsychotics, trazodone, beta-blockers

SAD Treatment Pearls
SSRIs (fluoxetine may not be as effective)
Exposure therapy good
Not effective: TCA, buspirone monotherapy, beta-blockers not for generalized SAD

Performance-only SAD: beta-blockers
- decrease perception of anxiety (tachy, sweating, blushing, tremor): propranolol 10-80mg, atenolol 25-100mg; taken 45min-1hr before situation

PTSD Treatment Pearls
Psychotherapy (CBT) is a must: trauma focused CBT to prevent conversion from acute stress (day 3 to 1 month) to PTSD/prevent chronic PTSD
Start drug therapy 3-4 weeks after trauma if no symptom improvements
Not effective: buspirone, bupropion, desimipramine
For augmentation: α1 antagonist: prazosin initial 1mg HS (max 16mg but limied by hypotension); may decrease nightmares/insomnia with reexperiencing sx
atypical antipsychotics (risperidone, quetiapine) may decrease hypervigilance and reexperiencing symptoms; newer evidence doesn't support use in PTSD
anticonvulsants/mood stabilizers (divalproex, carbamazepine, topiramate, lamotrigine) may decrease reexperiencing symptoms and aggression

Monitoring Therapy
time to response for most is 2-4 weeks; full effect 6-12 weeks
reaons why meds don't work: comorbid psychiatric disorders, intolerable ADEs (avoid rapid dose incr), underdosage, fail to wait to overcome delay in effect
partial response: ensure adequate time for response, maximize dose, add psychotherapy, add additional agent; augment based on symptoms
no response: ensure trial of 4-6 weeks; evaluate comorbidity; switch to another 1st-line or TCA, add psychotherapy; try alternative or adjunctive therapy
length of therapy: many need long-term GAD >12mo PD 12-24mo SAD usually life long PTSD >12mo after response

monitor s/s of serotonin syndrome/serotonin toxicity (hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes)

Pregnancy
- weigh risk of untreated anxiety vs. risk of medication; minimize number and dose of drugs
DOC: citalopram, fluoxetine, sertraline avoid: paroxetine, benzos (1st trimester at least; risk for floppy infant syndrome, infant withdrawal)

Adherence is key: nonadherence at 3 months is 50%; contributing factors: ADEs, delay to effect, improvement in symptoms, stigma

Patient education
- disease state: origin, stages, not crazy - expectations: delay to effect; residual symptoms, monitor improvement; ADEs - self-management (identify stressors)

Take Home Points
- symptoms of anxiety; anxiety differential; SSRI first-line, must give time to work; patient specific choice within class; use benzos appropriately; alt options

Sleep

1. Identify diseases, drugs, and behaviors that impact sleep patterns
2. Recognize symptoms and objective testing results; and recommend drug and non-drug treatment options, and monitoring
3. Educate on Sleep Hygiene and Stimulus Control methods 4. Screen for Obstructive Sleep Apnea using the STOPBANG tool
5. Select the best regimen given a patient case 6. Educate patients on sleep disorder basics and treatment options
7. Recognize and manage drug-related side effects and suboptimal response to therapy

Non-REM Stage 1: sleep initiation; intact voluntary muscle tone Stage 2: 50% of sleep time; muscle relax Stage 3/4: "Delta" or "Slow Wave Sleep"; *restorative*
REM skeletal muscle paralysis, Active brain function (↑HR BP, irreg breathing, ↓temp CO urine); critical for learning; dreaming stage; 20% of sleep time

Sleep Deprivation
- fatigue, depression, decreased new learning, obesity hormones (↓leptin signals full feeling; ↑ghrelin triggers appetite)
- hypertension, suppressed immune system; ↑glucose (DM risk); ↑C-reactive protein (heart disease risk)

Insomnia Disorder DSM-5 criteria
- dissatisfaction with sleep quantity or quality with at least one of the following:
  - difficulty initating sleep (long-sleep latency)
  - difficulty maintain sleep (more awakenings)
  - early-morning wakening with inability to return to sleep

AND
- complains of poor daytime functioning
- ≥3 nights per week
- ≥3 months duration
- despite adequate opportunity to sleep
- rule out secondary causes:
  - medical: breathing problems, stomach, thyroid, parkinson's, pain, cancer, dementia, epilepsy, etc
  - psychological: depression, anxiety, mania/hypomania, psychosis, substance abuse
  - medication: ADTs (SSRI MAOI TCA suppress REM; bupe stimulating); antineoplastic (interferon a, medroxyprog); levodopa amantadine; bronchodilators
    - CV (CCBs, lipophilic beta-blockers REM interference suppress melatonin); CNS stimulants; drug withdrawal (alcohol); endocrine (OCS, OC, progesterone)
  - environmental: bedroom noise, light, temp; timing of eating, exercise, caffeine/alcohol; circadian rhythm changes; daytime napping

Difficulty in failing and/or maintaining sleep: 2 wk sleep diary, observed by partner
- time to get to sleep ("sleep latency"); number and length of awakenings
- early morning awakenings - total sleep time ("sleep efficiency") - quality of sleep (daytime consequences)

Acute (episodic) Insomnia: <1 to 3 months
determine cause of insomnia + basic behavioral counseling (sleep hygiene and stimulus control) +/- intermittent medication
Treatment goals: resolve underyling causes, nondrug options, appropriate drug use (intermittent; NIH guidelines <4-6wk)
  - sleep hygiene: routine, environment (cool, dark, quiet); stop caffeine/nicotine/alcohol, exercise; adjust eating/drinking times
  - stimulus control: go to bed only when sleepy; use bedroom for sleep or intimacy; leave bedroom if unable to fall asleep within 15-20min; return when sleepy

Self-Treatment
alcohol: ↓SL ↑TST fragments sleep; evaluate chronic use;
antihistamines: ↑SM ↑TST no effect on SL, tolerance in 4-7 days of daily use; anticholinergic SE (dph 25-50mg, doxylamine 25mg)
melatonin 3-5mg qhs: ↓SL, regulates circadian rhythm not FDA regulated; CI pregnant/lactating; SE: fatigue dizziness HA irritability
St. John's wort: depression related insomnia induces 3A4
Co-Q10: CHF related insomnia, decreases nocturnal dyspnea
valerian: extracts with 400-900mg/d dosed 2hr before hs days-weeks to be fully effective; must wean off; may help SL

Chronic Insomnia: >3 months
affects more women, elderly, comorbid states, low socioecon, life stressors
Treatment goals: reestablish normal sleep pattern; address/treat secondary causes; reassess regularly, consider sleep study
  - start non-drug treatment options (target maladaptive behaviors); add intermittent drug therapy short term (schedule every 2-3 days prn)
ACP recommends CBT for insomnia (CBT-I) as initial treatment for chronic insomnia disorder.
  - as effective as drugs for persistent insomnia; sustainable results >6mo; individual/group therapy; weekly training 6-10 sessions

Benefits > Harm suvorexant (SM) eszopiclone (SO SM) zaleplon (SO) zolpidem (SO SM) triazolam (SO) temazepam (SO SM) ramelteon (SO) doxepin (SM)
Others: trazodone (SO SM; h>b) tiagabine (SO SM; h>b) dph (SO SM; b=h) melatonin (SO SM; b=h) l-tryptophan (SO SM; h>b) valerian (SO SM; b=h)

Sleep Onset (SO) - benzos: short-acting (triazolam) intermediate (estazolam, temazepam) - Z-hyponotics: zaleplon, zolpidem, eszopiclone - ramelteon
Sleep Maintenance (SM) or both: - benzos - Z-hypnotics - doxepin (Silenor 3-6mg) -orexin receptor antagonists (suvorexant, lemborexant)
Early Morning Awakening: Z-hypnotics short-acting: zaleplon, zolpidem SL (for use upon waking in middle of night)

Drugs linked to Parasomnias: zolpidem (sleep walking, sleep-related eating; case of 3A4 inhibition valproate); zaleplon overdose (sleepwalking); SA benzos, alcohol
Patient education: take <30min sleep; avoid high fatty meals (takes longer to kick); avoid alcohol; educate on intermittent vs. continuous use; lifestyle modification

Older adults: start with 1/2 adult dose; Z-hypnotics preferred; alternatives ramelteon 8mg, silenor 3mg, trazodone 25mg avoid benzos antihistamines, anticholi
Children: nondrug therapy first; ADHD change timing/drug; melatonin 1-5mg/dose (FDA) 2nd-line autism, circadian rhythm (blind)
  - development disorders (mental retardation, cerebral palsy) benefit in ↓SL; others (dph, clonidine)
Pregnant/lactating: DPH safest (cat B) on prn basis avoid doxylamine or hydroxyzine zolpidem (cat C0 if >30d of use during preg, risk for low BW/pre-term

Comorbid (nonFDA):
- without MDD or while initiating MDD drug therapy can try trazodone 50-150mg qhs <2wk treatment
- with MDD: TCAs (amitrip, doxepin) but they can suppress REM; mirtazapine (little effect on REM)
- with psychosis/schizophrenia: quetiapine, olanzapine, risperidone, lurasidone

Circadian Rhythm Disorders
light via eye → signals to suprachiasmatic nucleus (SCN) resetting circadian cycle daily
at dusk, SCN → SCN signals to pineal gland producing melatonin; important to trigger need to sleep, suppressed by bright light

DSM-5 Criteria
- alteration or misalignment between endogenous circadian rhythm and individual's required sleep-wake schedule
- disruption leads to excessive sleepiness and/or insomnia
- must cause poor functioning

Subtypes: Delayed (DSPS, owls)/Advanced (ASPS, larks)/Non-24hr sleep phase type; Shift work type

Treatment goals
short term (shift work type): improve sleep initiation, decrease excessive wake-time sedation;
long term: Delayed or Advanced sleep type: retrain to realign patient's circadian Non-24hr (blind) regulate s-w cycle consistenly

Nondrug: bright light therapy: suppress melatonin; for advanced (larks) use in PM; for delayed (owls) use in am; sleep hygiene
melatonin:
shift work: if >1week on new schedule; FDA approved ≥1.5hr before bed jetlag: 3-4 days treatment at night
DSPS: at dusk >1.5hr before bedime ASPS: at dawn, not rec'd older adults
tasimelteon for non-24hr s-w (blind); 20mg qhs w/o food as high fat meal less peak; may take weeks-months for full effect; avoid strong 1A2 inh and 3A4 inducers

Restless Leg Syndrome (Willis-Ekbomb Disease)

DSM-5 Criteria
- urge to move legs, usually accompanied by response to uncomfortable and unpleasant sensations in legs, with all of the following: Urge to move legs
  - begins or worsens during periods of rest/inactivity
  - partialy or totally relieved by movement
  - is worse in evening or night than day

AND
- occur ≥3x/week for ≥3 months
- complains of poor daytime functioning
- rule out mental/medical other effects

~12mill US, more women, worsens 70-80;
Pathophys: subcortical CNS dopamine deficiency; Fe important in dopamine transport/synthesis; impaired Fe storage = substantia nigra
secondary causes: systemic Fe deficiency; chornic diseases (parkinson's, RA, SLE, fibro, neuro, etc); pregnancy; ADTs (esp TCAs antipsychotics dph), antiemetic
  - rule out neurological exam (akathisia, nocturnal leg cramps, peripheral neuropathy); lab work: CBC, renal, iron/ferritin/transferrin

effects: SH (cigs, alc, caff, stress worsens), ↑SL ↑awakenings ↓sleep efficiency ↓QoL daytime drowsiness
Definitions
  intermittent: <2x/wk; troublesome requiring treatment
  chronic persistent: ≥2x/wk; requiring daily treatment
  refractory: unresponsive to monotherapy due to low efficacy, augmentation, SE

Treatment goals: alleviate primary sx, improve sleep quality and quatity and QOL
Lifestyle: avoid alc, caf, cigs, stress; regular exercise; try warm bath 2hr qhs; massage stretch, increase dietary iron intake
Drugs:
  intermittent RLS/WED: levodopa-carbidopa (IR or CR qhs) prn; benzos (clonazepam daily); low-potency opioid prn (tramadol, codeine)
  chronic persistent RLS/WED: non-ergot dopamine agonist (pramixpexole, ropinirole, rotigotine patch); gabapentin or pregabalin
  refractory RLS/WED: re-evaluate, check iron stores and replenish; consider combo therapy (dopamine agonist, gaba/pregabalin, opioid, benzo)

<u>dopaminergic agonists</u>
ropinirole (Requip): hepatic and renal clearance; initial 0.25mg qd, titrate q2-3d to 1-3mg/day
pramipexole (Mirapex): renal clearance; initial 0.125mg qd, titrate to 0.375mg/d
  - dosed 2 hours before RLS sx start; neither ER formulation has FDA indication (those are for parkinson's)

rotigotine (Neupro): hepatic clearance; initial 1mg/24hr, titrate by 1mg weekly to max 3mg/24hr; wean off when dc'ing
DOC when: increased fall risk, severe sx of RLS, excess weight, metabolic syndrome or OSA, comorbid depression

<u>alpha-2-delta calcium channel ligands</u>
gabapentin enacarbil (Horizant): 600mg at 5pm ER (prodrug); dose adj <60 renal - not interchangeable with gabapentin - FDA approved RLS
gabapentin 800-1800mg/d in div doses; late afternoon to 2hrs before bed; pregabalin titrate 150-450mg/day in dd
DOC: sleep disturbance or comorbid insomnia, painful RLS, comorbid pain syndrome, hx or current impulse control disorder; comorbid GAD

Others oxycodone pain prn; benzos to sleep thru sx (clonazepam ↓ periodic limb movmeents PLM/hr)
Additional: *iron status (treat if Ferritin <75mcg/L); ferrous sulfate 325mg bid (with vit c 100-200mg with each dose for acidic absorption in GI)
  - check serum ferritin q3mo; dc once ferritin >75 and iron saturation >20%

Pregnancy: nonpharm; maintain oral iron suppl; opioids used sparingly (2^{nd}-3^{rd} trim); educate on expected time course; avoid in breastfeeding
ESRD/HD: vit c 200mg and vit E 400mg suppl; prefer ropiniole; avoid pramipexole; avoid or renally dose alpha-2delta ligands; exercise
hepatic/alcohol/abuse: avoid ropinirole, use caution with rotigotine patch

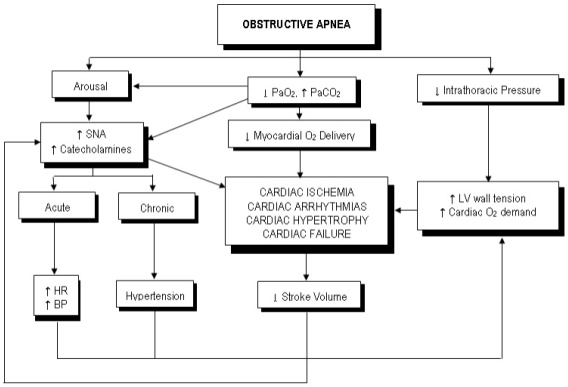
RLS: women>men, worsens till age 70-80s; etiology CNS dopamine impairment; triggers cigs, alc, caff; diagnosis by symptoms and exclusion
PLM: women=men; incidence incr with age; etiology CNS dopamine impairment; triggers cigs, alc, caff; diagnosis by Polysomnogram (PSG) and sleep study
  - polysomnogram during sleep ≥4 consectuive involuntary movements 0.5-5 sec separated by 20-40sec; movements less in in stage 3/4 and REM sleep

Obstructive Sleep Apnea Hypopnea (OSAH)
Pathophys: complete airway obstruction .. breathing ceases .. ↓O2 ↑CO2 .. brain signals to arouse .. pharyngeal dilator muscle tone restored .. loud snore/gasp .. breathing resumes
Symptoms apnea: cease to breathe for >10seconds hypopnea: reduced respiratory airflow by 30%; drop of 4% of pulse-ox
daytime: sleepiness/fatigue (EDS: excessive daytime sedation); morning HA, muscle aches; drymouth nasal congestion, cognitive impair; ↓libido ED, depression
nighttime: loud snoring, witnessed apneas, disrupted sleep, nocturia, snorts/gasps leading to arousal

Apnea-Hypopnea Index (AHI) = total # apneas + hypopneas per hour mild-AHI 5-14 moderate-AHI 15-30 severe-AHI >30

DSM-5 Criteria
- evidenced by PSM (polysomnography) ≥5 obstructive apneas or hypopneas/hour and either of the following
  - nocturnal breathing disturbances
  - daytime sleepiness, fatigue, unrefreshing sleep
OR
- evidenced by PSM ≥15 obstructive apneas and/or hypopneas/hour of sleep regardless of accompanying symptoms

Epidemiology: 85% undx; "obstructive" risk factors: male>female, age >40yo, obese, hypothyroidism, smoker, nasal/anatomic narrowing; alc/sed use; genetic AA
Untreated cardiac consequences: cardiac ischemia, arrythmias, hypertrophy, failure; hypertension



STOP BANG: OSAH screening questionnaire: If yes to ≥3 of 8 = high risk of OSA
Do you **S**nore loudly (louder than talking or loud enough to be heard through doors)?
Do you often feel **T**ired, fatigued, sleepy during daytime?
Has anyone **O**bserved you stop breathing during your sleep?
Do you have or are you being treated for high blood **P**ressure?
BMI ≥35kg/m2
Age>50yo
Neck circumference >40cm (15¾in)
Gender Male?

Treatment goals:
- improve airway patency; decreased apnea/hypopnea frerq; improve quality/quantity sleep
- decrease excessive daytime functioning; avoid long-term complications

Nonpharm treatment: wt reduction- wt loss in obese (guideline); severe OSA not responding to CPAP can try surgery or radiofreq ablation therapy
Mild OSA (AHI 5-14): positional therapy (guideline), oral appliances
Mod-Severe OSA (AHI >15): treatment of choice CPAP: Continuous Positive Airway Pressure

Drug treatment: avoid CNS depressants
Z-hypnotics: add to improve <u>initial</u> CPAP acceptance
modafinil for persistent excessive daytime sedation (EDS) after effective CPAP
topical nasal corticosteroids; benefit with concurrent rhinitis

Monitoring: adherence to CPAP
- use of respiratory depressants off CPAP
- improvement of pre-CPAP sx: EDS, morning HA, hypertension, cognition, muscle aches, mood, nasal congestion, libido/ED

Li
Sleep 4-6 cycles each 60-90min
Stages 1-4 (NREM) Stage 1 drowsiness, very light sleep 5% Stage 2 light sleep 50% Stage 3/4 deep (delta) sleep 20% Stage 5 (REM) dreams 25%
hypnotics decrease time spent in stages REM and 3/4 and increase time in stage 2

Parkinson's Pcol
Pathophysiology
Parkinsonism – cluster of symptoms
- bradykinesia: slowness/poverty of movement
- muscular rigidity
- resting tremor (usually reduces during voluntary movement)
- impairment of postural balance (leads to gait walking disturbances and falling)

Primary (Parkinson's Disease): idiopathic/classic PD; cause unknown, no cure; most common form of parkinsonism
Secondary (reversible)
- adverse effect of drugs: antipsychotic drugs; reserpine, tetrabenazine (depletes dopamine)
- stroke (loss of blood supply to brain)
- repetitive head trauma (dementia pugilistica; boxers)
- viral infection (postencephalitic parkinsonism)

Pathophysiology
- loss of dopaminergic neurons in the substantia nigra (midbrain, close to SC); substantia nigra is the source of DA neurons
- characteristic pathology: Lewy Bodies (protein aggregates)

Basal ganglia = collection of brain structures; function is planning and programming of movement
- modulatory side loop - regulates flow of info from cerebral cortex to motor neurons (SC)
- parts of basal ganglia important: - striatum = caudate nucleus + putamen - substantia nigra - globus pallidus, subthalmic nucleous, nucleus accumbens
- basal ganglia deals with planning of movement; lose the ability to smoothly execute certain movements

Dopamine
location: synthesized in neurons originating in the substantia nigra OR ventral tegmental area (in brainstem); axons of these neurons project throughout brain
these neurons project to striatum (nerve terminals release dopamine); in PD, loss of dopaminergic input to striatum
overall, dopamine acts as an inhibitor neurotransmitter
role: movement, reward, others
synthesis: precursor tyrosine → L-DOPA (via tyrosin hydroxylase) → dopamine (via aromatic L-amino acid decarboxylase aka dopa decarboxylase)
receptors: D1-like (D1 D5); D2-like (D2 D3 D4); all metabotropic G-protein coupled
D1-like: excitatory; activation of adenylate cyclase (↑cAMP)
D2-like: inhibitor; inhibition of adenylate cyclase (↓cAMP); activation of K+ potassium channels; inhibition of voltage-sensitive Ca++ calcium channels
termination of action: reuptake by DA transporters terminates action in synapse; transporters primarily located in presynaptic terminal
metabolism: monoamine oxidsase (MAO), catechol-O-methyltransferase (COMT)

Summary
- dopamine content of substantia nigra and striatum in PD patients is very low; symptoms of PD appear when about 60-80% of dopamine is lost
- eventually almost complete loss of dopamine neurons from substantia nigra, and nerve terminals in striatum; usually <10% of normal PD (postmortem)
- neuronal degeneration and depigmentation and appearance of intracellular inclusions (Lewy bodies) in dopamine neurons

Nigrastriatum pathway:
- dopamine normally inhibits inhibitory GABA neurons in striatum; predominately due to activation of inhibitor D2 dopamine receptors on GABA neurons
- acetylcholine, an excitatory neurotransmitter in striatum, is relatively unaffected in PD

Consequences of dopaminergic neuron degeneration: loss of dopamine in PD therefore results in increased inhibitory signaling mediated by GABA neurons
- i.e., no dopamine available to bind to the inhibitory D2 receptors, so there is increased release of GABA from GABA neurons
- the imbalance of inhibitor neurotransmission in basal ganglia leads to motor symptoms

Concept is important with respect to the therapeutic effectiveness of levodopa
- lesions of the nigrostriatal tract or chemically-induced depletion of dopamine in experimental animals causes symptoms resembling PD
- brain has compensatory mechanisms to try to preserve transmission in spite of neuronal loss
- increase in dopamine receptors: 'denervation hypersensitivity' - hyperactivity of remaining dopaminergic neurons; increased rate of transmitter turnover

Pharmacology

levodopa

- dopamine precursor; ultimately increases DA release in striatum
- most effective treatment for PD; ~80% effective at beginning of treatment, improves rigidity and hypokinesia, increases life expectancy
- dopamine does not cross BBB
- levodopa uses aromatic amino acid transporter to cross intestines and brain
- ADEs
  - involuntary writhing movements (dyskinesia)
    - most patients within a few years
    - face and limbs can be severe
    - decrease if decrease dose, but then become rigid again
    - narrow margin between beneficial and unwanted motor effects with long-term treatment
  - rapid fluctuations in clincal state
    - hypokinesia and rigidity may suddenly worsen for few minutes to hours and then improve again
    - reason not known: may be related to progressive loss of dopamine terminals
  - schizophrenia-like syndrome (psychosis: delusions and hallucinations); compulsive behaviours, confusion, disorientation, nightmares
    - new antipsychotic approved: pimavanserin (Nuplazid)
- with time, effectiveness of levodopa declines likely due to further loss of dopamine neurons with disease progression
  - part of levodopa action requires presence of some functional dopamine terminals
  - hyperactivity of remaining dopamine terminals helps increase conversion of levodopa to dopamine

levodopa/carbidopa (Sinemet)
levodopa/carbidopa/entacapone (Stalevo)

carbidopa

- peripheral dopa decarboxylase inhibitor
- carbidopa does not cross BBB; only inhibits peripheral dopa decarboxylase in periphery
- about 95% of levodopa would be converted to dopamine in periphery without carbidopa
- reduces dose of levodopa needed by 10-fold; diminishes adverse effects of peripheral conversion of levodopa to dopamine (GI and cardiovascular effects)

COMT inhibitors

entacapone (Comtan), opicapone (Ongentys), tolcapone (Tasmar) tolcapone increased risk of hepatic failure (monitor liver function)

- inhibit COMT in periphery
- coadmin with levodopa provides for more sustained levels of levodopa and may increase amount that can cross BBB

Dopamine agonists

pramipexole (Mirapex), ropinirole (Requip), bromocriptine (Pardolel)

- activates D2 dopamine receptors directly; mimic endogenous actions of dopamine by activating D2 dopamine receptors directly
- unlike levodopa, does not require enzymatic conversion to dopamine, does not compete with amino acids for intestinal or brain transport
- may be used as monotherapy in early PD; combined with levodopa in more advanced stages; use to decrease dose of levodopa if needed

apomorphine: subcutaneous injection

- indicated for acute, intermittent treatment of hypomobility, “off” episodes in advanced PD; use antiemetic therapy simultaneously (trimethobenzamide Tigan)

MAO-B inhibitors

selegiline (Deprenyl) amphetamine metabolite SE insomnia, rasagiline (Azilect) not metabolized to amphetamine, safinamide (Xadago) newest MAO-B

- MAO-B isoenzyme predominant form in striatum and responsible for most of metabolism of dopamine in brain
- overall generally modest effect on symptoms; generally used as addons to levodopa and/or as early monotherapy
- tyramine restrictions not required since MAO-B is lower in GI (and liver) so less involved in dietary metabolism of amines (including tyramine)

amantadine

- increase dopamine release: releases endogenous dopamine and/or blocks dopamine reuptake into nerve terminals
- blocks glutamate receptors also (NMDA subtype); indirectly affect dopamine release? decrease neurotoxicity (excitotoxicity)?
- has anticholinergic effects but not working on those receptors; also used as antiviral agent

Anticholinergic

benztropine (Cogentin), trihexylphenidyl (Artane)

- block excitatory cholinergic transmission in basal ganglia; compensate for loss of dopaminergic inhibtion by decreasing cholinergic excitation
- used for mild symptoms, tremors; less effective than dopaminergic drugs
- can be used to treat antipsychotic-induced parkinsonism
  - antipsychotics block D2 receptors so less effect of dopaminergic anti-PD drugs; also dopaminergic anti-PD treatments may exacerbate psychosis

Adenosine A2A receptor antagonist

istradefylline (Nourianz)

- adjunctive treatment to levodopa/carbidopa in adults with PD experiencing “off” episodes
- adenosine formed from metabolism of ATP (ENT=equilibrative nucleoside transporter)
- the purine P1 receptor family comprises 4 adenosine receptor types (all metabotropic G protein): A1 A2A A2B A3
  - A2A highly enriched in striatum and functionally oppose D2 receptors

Parkinson's Disease

Be familiar with the clinical presentation of Parkinson disease
Given a patient case, determine the Hoehn and Yahr Staging of Disease Severity
Given a patient case, devise an appropriate treatment regimen for Parkinson disease based on specific patient characteristics
Design an appropriate monitoring plan for any of the treatment options for Parkinson disease
Determine the important patient counseling points for each treatment option for a patient with Parkinson disease
Given a patient case, recommend treatment of the motor complications of PD
Describe the non-motor symptoms of PD

Epidemiology: M>F, 40k cases/yr, begins 55-65yo; 5-10% relative with PD (genetics?)
Pathology: dopamine nigrostriatal tract; severity correlates with degree of neuronal loss; sx begin with 75% decrease in number of neurons in substantia nigra
- Lewy bodies: neuronal, cytoploplasmic filamentous aggregates composed of presynaptic protein **alpha-synuclein**; develops deeper area of brain, then cortex

Differential Diagnosis: infectious (encephalitis), drug-induced, toxic, degenerative, Alzheimer's disease
Clinical Presentation: Classic features (Cardinal manifestations) **TRAP**: **T**remor **R**igidity **A**kinesia (or bradykinesia) **P**ostural instability
- also masked facies (hypomimia), hypophonia, micrographia, gait abnormalities (shuffling, leg dragging, festination, propulsion/retropulsion)

Non-motor symptoms of PD
neuropsychiatric: dementia, hallucinations, depression, anxiety
autonomic: orthostatic hypotension, urinary urgency/frequency, paroxysmal sweating, seborrhea, xerostemia
sleep disorders: REM sleep behavior disorder, RLS GI: drooling of saliva, dysphagia, constipation Falls fatigue, diplopia, blurred vision, weight loss/gain

Unified Parksinson's Disease Rating Scale (UPDRS): used to define the degree of disability in motor and some non-motor symptoms
part 1: evaluation of mentation, behavior, mood
part 2: self evaluation of ADLs (speech, swallowing, handwriting, dressing, falling, salivating, turning in bed, walking, cutting food)
part 3: *clinician-scored motor evaluation
part 4: Hoehn and Yahr staging (disease severity)
Stage I—unilateral Stage II—bilateral, no postural abnormalities Stage III—bilateral, mild postural abnormality
Stage IV—bilateral, with postural abnormality Stage V—severe, fully developed disease (pt chair/bed bound)
part 5: Schwab and England ADL scale

Hoehn and Yahr staging (disease severity)

Treatment goal: maintain patient independence, ADL, quality of life by:
- minimizing patient symptoms, minimize development of motor complications, limiting med-related ADEs, on-off terminology (off=PD not controlled)
- nonpharm: group support, education, exercise, nutrition (fiber, calcium, protein)

Motor complications associated with therapy
- more common with levodopa than any other options; 30% patients starting levodopa will develop motor complications in 3-5 years; >50% in 4-6 years
- correlation between dose and duration of levodopa and development of motor complications
- due to more pulsatile stimulation of dopamine receptors and decreased number of remaining dopaminergic neurons?

Motor Complications
Motor Abnormalities - wearing off - on-off fluctuations - freezing
Dyskinesias - choreiform (jerky, rapid, repetitive, involuntary movements) - dystonia (uncontrollable muscle contractions)

Considerations before initiating therapy for PD: age, cognitive impairment, bradykinesia/postural instability, chronic comorbidities, functional impairment
- do they have cognitive impairment?
- do they have significant bradykinesia and/or postural instability?
- how old are they?
- do they have any other significant chronic diseases?
- how are symptoms impacting daily life of patient? (functional impairment)
  - degree of functional impairment: - any dominating classic feature? - affecting dominant hand? - patient still working? - affecting ADLs?

dyskinesia: abnormality or impairment of voluntary movement.
akinesia: loss or impairment of the power of voluntary movement.
bradykinesia: slowness of movement.

Part 3

Part 4
Motor complications (wearing off, on-off fluctuations, freezing)
- must assess: - adequacy of peak response - duration of that response - when the motor difficulties occur in relation to dosing of meds

Wearing Off
- loss of mobility or dexterity near the end of the dosing interval
- interventions:
  - more frequent dosing of Sinemet
  - addition of dopamine agonist, MAO-B inhibitor, COMT inhibitor

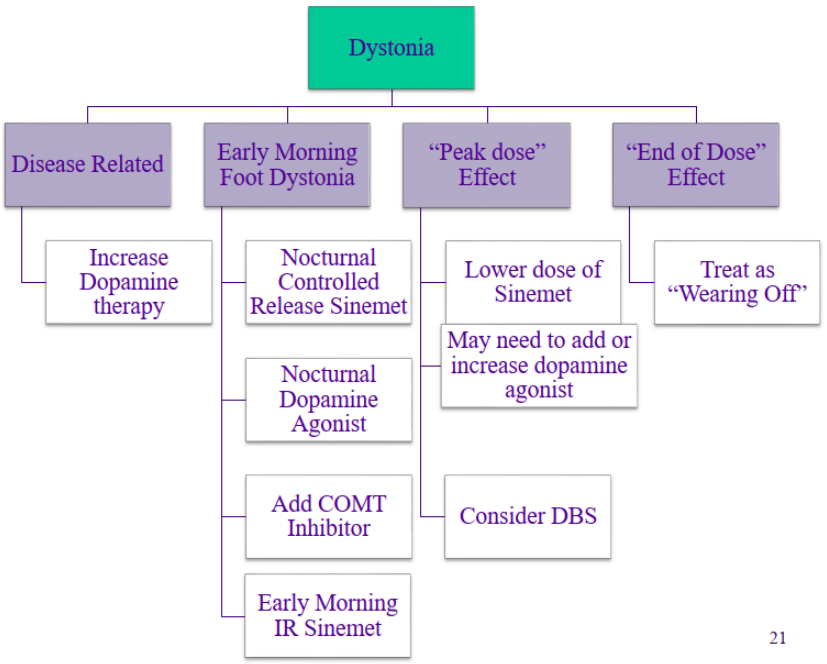
On-Off Fluctuations
- unpredictable and generally sudden shifts between on and off periods; not related to dosing
- interventions:
  - addition of dopamine agonist
  - use of liquid Sinemet in small doses at 60-90 min intervals

Freezing Of Gait (FOG)
- transient inability to initiate movement
- increasing dose tends to aggravate freezing, therefore trial of dosage reduction should be attempted if timing makes sense that is drug related
- most commonly, nonpharm first tried
  - strips of colored non-slip tape on floor in living room
  - other visual cues – laser cane
  - movement strategies including shifting weight, making wider turns concentrating on taking larger steps forward
- apomorphine

Dyskinesias
Choreiform: involuntary movements involving neck, face, trunk, lower/upper extremities
Dystonia: sustained muscle contractions; often occurring as clenching of toes or involuntary turning of foot
- can be due to disease process or related to medications
- intervention for disease related
  - bedtime dose of Sinemet CR or dopamine agonist
  - end of dose dystonias: use Sinemet CR or add dopamine agonist
- intervention for medication-related
  - usually at peak so decrease individual doses of Sinemet

Peak Dose Dyskinesias
- interventions
  - lower individual doses of Sinemet
  - amantadine (may need doses >300mg/day); usually after lowering Sinemet dose
  - may need to add dopamine agonist or COMT inhibitor to maintain sx control
  - switching to Sinemet CR tends to make dyskinesias worse

Diphasic Dyskinesias
- cause not clear; may have to do with differeing receptor sensitivity of dopamine stimulation
- interventions for mild (only try one at a time)
  - more frequent dosing of Sinemet
  - add dopamine agonist, amantadine, or COMT inhibitor; liquid Sinemet
- interventions for severe
  - overlapping doses
  - predict Off times



Psychiatric/Behavioral Disorders

- Dementia – about 50% of patients will develop to some degree
- First look for drugs that may exacerbate dementia (anticholinergics, selegiline, amantadine, dopamine agonists, TCAs)
- Cholinersterase inhibitors have been used and can be an option for demenitia in PD pts

Hallucinations and Psychosis- may be due to dementia or more than likely, the PD drug therapy

- Clozapine or Quetiapine specifically studied in this population
- Caution against use of olanzapine as has shown bit higher chance of worsening motor symptoms
- Pimavanserin (Nuplazid®) – approved in 4/2016 for treatment of hallucinations or delusions associated with PD psychosis

- Depression – occurs in about 35-40% of pts
- Nortriptyline, desipramine, venlafaxine, citalopram and paroxetine have shown positive results in PD pts with diagnosed depression
- Sleep Disorders – mostly fragmented sleep
- Rapid eye movement (REM) sleep behavior disorder (RBD) occurred is some PD patients and benzodiazepines can treat, but use not supported by AAN practice parameters for nonmotor symptoms in PD
- Chamberlin KW, Sahbani Q. Key cogs in the management of Parkinson's disease. Drug Topics 2016 CE article at drugtopics.com
- Weight Loss – 50% of PD pts experience during course of their illness
- More than likely due to dopaminergic medications

Autonomic Disorders

- bladder and sphincter disturbances - constipation - diaphoresis - orthostatic blood pressure changes - sexual disturbances - paroxysmal flushing

Falls

- Insufficient motor control? - Increasing postural instability? - Orthostatic hypotension from PD or medications? - Other drug side effects such as sedation?

Key Concepts

Continuous surveillance of motor and non-motor symptoms – often necessitates somewhat frequent therapy adjustments
Treatment should be initiated when the disease begins to interfere with ADLS, employment, or quality of life
Anticholinergic medications can be useful for mild tremor predominant symptoms, but cautious use in older adults
Amantadine and MAO-B inhibitors can provide some symptomatic benefit as monotherapy but less than that of dopamine agonists or Sinemet
Sinemet is the most effective medication for symptomatic treatment
Most Sinemet treated patients will develop motor complications (fluctuations and dyskinesias most commonly)
MAO-B inhibitors, COMT inhibitors and Istradefylline are useful add-on therapies to attenuate motor fluctuations in Sinemet treated patients
Amantadine is a useful add-on agent to attenuate dyskinesias
Dopamine agonists are effective, associated with less risk of developing motor complications, but more risk of causing psychiatric symptoms, such as hallucinations and impulse control disorders or worsen underlying cognitive deficits

Antipsychotics Pcol

Pyschosis
- describes a mental state (not a specific disorder); state in which individual appears to have lost touch with reality
  - disruption of reality test | ability to understand world
- can be associated with many conditions: schizophrenia; delirium | dementia | AD | depression; adverse effects; endocrine dysfunction; mania (bipolar disorder)

Schizophrenia is the most common cause of chronic psychosis
- active psychosis (e.g. delusions and hallucinations); - disturbance of logical thought process and deterioration of social and occupational function
  - delusion: belief not based on fact or reality (types: persecutory most common, grandiose, religious, somatic, nihilistic, sexual)
  - hallucination: perception disturbance in sensory experiences of the environment (types: auditory most common, visual, olfactory, tactile)
- clinical presentations: all characterized by chronic distrubances in perception and integration of reality; mostly show disabling deficits in cognition and motivation
- categories of symptoms of schizophrenia
  - positive symptoms (mesolimbic): new mental phenomena, which unaffected people normally do not experience (hallucinations, delusions)
    - hallucinations, delusions, thought disorders, disorganized speech, bizarre behavior, insomnia, combativeness
  - negative symptoms (mesocortical): loss of normal mental functions; amotivation and social withdrawal
    - affective flattening, alogia, apathy, amotivation, anhedonia, asocial behavior, inattentiveness
- genetic of schizophrenia: 1% prevalence; 12% if parent has schizophrenia; 50% concordance in identical twins (monozygotic); 7-12% in fraternal twins (dizygotic)
  - risk of schizophrenia reflects status of biological rather than adoptive parents = strong genetic contribution

Pathophysiology
- multiple genes interact to increase vulnerability to schizophrenia; difficult to identify these risk-related genes; non-genetic factors convert vulnerability to illness
- non-genetic factors: may include random development processes
  - even identical twins do not have identical sulcal and gyral patterns in cortex; certain amount of chance in wiring
  - environmental insults? malnutrition, in utero viral infection
- anatomical correlates of schizophrenia
  - decreased brain volume and enlarged ventricles
  - overall gray matter volume reduced by 10-15%; microscopically, evidence of 'misplaced' neurons in cortex suggests defective cell migration during develop
- functional neuroanatomical studies: decreased metabolic activity in prefrontal cortex
  - prefrontal cortex is the area of brain important for higher cognition and working memory; attention planning motivation

A general model integrating the concepts of schizophrenia
Etiology: multiple convergent factors (e.g., DNA, gene expression, viruses, toxins, nutrtion, birth injury, psychological experiences) →
→Pathophys: brain development from conception to early adulthood (e.g., neuron formation, migration, synaptogenesis, pruning, apoptosis, activity dependent changes)
  →antatomic and functional disruption of neural connectivity and communication
  →impairment in a fundamental cognitive process
→Phenomenology: impairment in one or more second-order cognitive processes (e.g., attention, memory, language, emotion)
→Phenomenology: symptoms of schizophrenia (e.g., hallucinations, delusions, negative symptoms, disorganized speech)

Dopamine
- drugs tha increase dopamine can cause psychotic symptoms (amphetamine, cocaine)
- significant innervation of prefrontal cortex by dopaminergic neurons
- some evidence of changes in dopamine receptor/release in schizophrenia
- antipsychotic drugs are D2 dopamine receptor antagonists

ventral tegmental area (VTA): cell bodies of dopamine neurons that project axons to many brain regions including frontal cortex and limbic (emotional control)
mesolimbic: emotional control (involved with positive symptoms of schizophrenia); hyperdopaminergic
mesocortical: executive function, planning, logic (involved with negative symptoms of schizophrenia); hypodopaminergic

There are actually 4 dopaminergic subsystems:
• The nigrostriatal pathway (motor control)-Parkinson's disease
• The mesolimbic pathway (hyperdopaminergic)
  - Increase in dopamine in this pathway postulated to causes positive symptoms of schizophrenia such as: - hallucinations - delusions
• The mesocortical pathway(hypodopaminergic)
  - Deficit in dopamine in this pathway postulated to causes negative symptoms of schizophrenia such as: - executive function - affective - difficulty thinking
• The tuberoinfundibular pathway- regulation of prolactin secretion.

Genetic/Environment factors (GxE)
"It is proposed that a dysregulated, hyperdopaminergic state, at a "brain" level of description and analysis, leads to an aberrant assignment of salience to the elements of one's experience, at a "mind" level.
Delusions are a cognitive effort by the patient to make sense of these aberrantly salient experiences, whereas hallucinations reflect a direct experience of the aberrant salience of internal representations.
Antipsychotics "**dampen the salience**" of these abnormal experiences and by doing so permit the resolution of symptoms. The antipsychotics do not erase the symptoms but provide the platform for a process of psychological resolution."

Pharmacology
Block of D2 dopamine receptors is correlated to antipsychotic action
  - requires >60% blockade for antipsychotic effect
Antipsychotics also block histamine, adrenergic, acetylcholine; inhibition of these receptors contribute to ADEs (off-target effects)

First Generation Antipsychotics (FGA): "typical" or "conventional" antipsychotics
Second Generation Antipsychotics (SGA): "atypical" antipsychotics
Strong correlation for D2 receptors and weak or no correlation for D1 (and other transmitters): lead to idea that D2 blockade is important for therapeutic effect.

Partial dopamine agonists
  - block overstimulated receptors and stimulate underactive receptors;
    - act as 'dopamine stabilizer'
  - theory that these drugs decrease DA activity in overactive dopamine systems while increasing DA activity in regions of brain where DA activity is low
  - have not been shown to have increased efficacy relative to FGA or SGA
- a partial agonist acts on same receptor system as the full agonist, but cannot produce as large an effect because it has lower maximal efficacy
- a partial agonist can act as an antagonist or full agonist (when both are combined, the effect of the full agonist is inhibited)
e.g. aripiprazole activity at D2 receptors in presence or absence of dopamine
  - a partial D2 agonist thus inhibits effects of DA and reduces stimulation at D2 receptor only to the extent of its own capacity as an agonist
  - haloperidol, an antagonist without agonist activity, completely antagonizes D2 receptor activation

Adverse Effects

Drug-induced movement disorders (DIMD)

Extrapyramidal symptoms (EPS)

akathisia: uncontrollable restlessness

dystonia: involuntary movements (muscle spasms, protruding tongue, etc.)

parkinsonism: symptoms resembling PD

- result directly and indirectly from D2 receptor blockade (>80% blockade)
- disruption of dopamine signaling (D2 receptor mediated) in substantia nigra → striatum pathway important for motor function
  - strength of EPS generally correlates with D2 receptor potency
  - *high affinity D2 binding generally leads to stronger EPS

Tardive dyskinesia

involuntary movements, usually face and tongue, trunk and limbs; develops after months or years; disabling and can be irreversible

- may be due to increase in number and/or sensitivity of D2 receptors in striatum

Treatment: valbenazine (Ingrezza), deutetrabenazine (Austedo)

- vesicular monoamine transporter 2 (VMAT2) inhibitors
- depletion of monoamines would decrease excessive dopamine signaling that may be causing dyskinesia

- generally, SGAs have lower propensity for EPS and tardive dyskinesia compared to FGAs
  - generally lower affinity of SGA for D2 receptors than FGA
- based on low EPS profile of the first SGA, clozapine, the newer SGAs were designed with a similar receptor binding profile
- all antipsychotics are D2 dopamine antagonists, while most SGAs were designed to also block 5HT2A serotoinin receptors (like clozapine)
  - blocking 5HT2A receptors in striatum releases neurons from serotonin inhibition of dopamine release (nigrostriatal pathway)
  - increase striatal dopamine release would help counteract dopamine D2 receptor blockade

ADEs of antipsychotics

- hyperprolactinemia: breast swelling, lactation, pain
  - dopamine D2 receptors normally inhibit prolactin release; antipsychotics would increase release of prolactin from pituitary
- orthostatic hypertension via alpha-adrenergic inhibition
- dry mouth, blurred vision, urinary retention, constipation, other atropine-like effects due to muscarinic receptor inhibition
- sedation, weight gain due to histamine receptor inhibition
  - weight gain associated with inhibition of H1 and 5HT2C, likely in hypothalamus; important role of hypothalamus in regulating appetite
- hyperglycemia, hyperlipidemia: weight gain may contribute to these effects; other mechanisms?

Other issues

- can take several weeks for full anti-psychotic effect
  - sedation is immediate, so can be used acute behavioral emergencies; relationship of delayed effects to clinical response not understood
- do not control negative symptoms or cognitive issues well
- effective in 70% of patients; other 30% are 'treatment resistant' (unknown reason)

Type	**Manifestations**	**Mechanism**
Autonomic nervous system	Loss of accommodation, dry mouth, difficulty urinating, constipation	Muscarinic cholinoceptor blockade
	Orthostatic hypotension, impotence, failure to ejaculate	α-Adrenoceptor blockade
Central nervous system	Parkinson's syndrome, akathisia, dystonias	Dopamine-receptor blockade
	Tardive dyskinesia	Supersensitivity of dopamine receptors
	Toxic-confusional state	Muscarinic blockade
Endocrine system	Amenorrhea-galactorrhea, infertility, impotence	Dopamine-receptor blockade resulting in hyperprolactinemia
Other	Weight gain	Possibly combined H_1 and 5-HT_2 blockade

Clozapine

- superior in treatment-resistant patients; distinguishes clozapine from other antipsychotic drugs
- agranulocytosis: rare and serious idiosyncratic reaction; decrease in WBC, reduced ability to fight infection (1-2% of users); requires regular monitoring

pimavanserin (Nuplazid)

- does not block D2 receptors; inverse agonist and antagonist activtity at 5HT2A receptors and lesser extent 5HT2C.
- new atypical antipsychotic for treatment of hallucinations and delusions associated with Parkinson's disease

Other uses of Antipsychotic Drugs

psychomotor agitation and severe anxiety (**chlorpromazine** and **haloperidol**)

agitation and restlessness in the elderly (**risperidone**), although this is highly questionable

psychosis associated with Parkinson's disease (**primavanserin**)

restlessness and pain in palliative care (**levomepromazine**)

nausea and vomiting (e.g. **chlorpromazine** and **haloperidol**) reflecting antagonism at dopamine, muscarinic, histamine and possibly 5-HT receptors

motor tics and intractable hiccup (**chlorpromazine** and **haloperidol**)

antisocial sexual behaviour (**benperidol**)

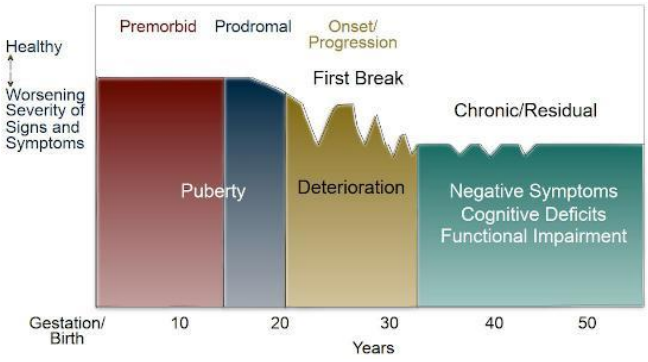
involuntary movements caused by Huntington's disease (mainly **haloperidol**)

Schizophrenia

Pathophysiology
not fully understood; many other neurotransmitters involved (glutamate, 5HT, ACh, GABA)
--dopamine too high in mesolimbic pathway = positive symptoms (hallucinations, delusion, auditory)
--dopamine too low in mesocortical pathway = negative symptoms (affective, difficult to make decisions, cognitive)

Risk factors: genetics, prenatal stress (maternal, infections); stressors (marijuana, drugs, trauma, immigrants, situational, medications)

DSM-V Diagnosis: Schizophrenia
A. Two or more of the following are present for at least 1 month, (one must be A-C):
  A. Delusions
  B. Hallucinations
  C. Disorganized speech
  D. Disorganized or catatonic behavior
  E. Negative symptoms
B. Decrease in social/occupational functioning
C. Continuous signs of disturbances for at least 6 months
D. R/O psychotic or developmental disorders
E. Disturbance not due to a drug of abuse, medication or general medical condition



Clinical Presentation

Differential Diagnoses
- Schizophreniform disorder (symptoms <6 months)
- Schizoaffective disorder (2 weeks of antipsychotic, 2 weeks of mood disorders)
- Mood disorder with psychotic features
- Psychotic disorder secondary to dementia, delirium, general medical condition
- Pervasive developmental disorder
- Cluster A Personality disorders (schizoid, schizotypal, paranoid personality disorder, delusional disorder)
- Medical disorders (neurosyphilis, thyroid disorders)
- Substance-induced psychosis or withdrawal-induced

Prognosis
Course can be variable:
  - Majority: chronic relapsing/remitting
  - Poor responses to medication (~30% show little response)
Factors associated with good prognosis:
  - Female
  - Rapid (vs. insidious) onset of symptoms
  - Older age of first episode
  - Predominantly positive (rather than negative) symptoms
  - High pre-illness functioning
  - Support structure

General Approach to Treatment
Stabilize acutely psychotic patient
Initiate treatment with an antipsychotic: - Minimize symptoms - Minimize medication side effects - Prevent relapse, maximize function
Choice of antipsychotic based on multiple factors
  - All antipsychotics are equally effective on positive symptoms if used in 'equipotent' or 'therapeutic' doses
  - Exception: clozapine has superior efficacy
Maintain a patient on antipsychotic treatment: - Likely lifelong medications, high relapse rates without
Link with appropriate level of mental health services: Psychiatry, Counseling, Nursing, Primary care, Case management (benefits, housing, transportation, goals), Vocational rehabilitation/ occupational therapy, Pharmacy (adherence packaging, injectable antipsychotics, MTM)

Negative symptoms
Diminished expression
  - Affective flattening: Unchanging facial expression Little spontaneous movement Little use of expressive gestures Poor eye contact Affective non-responsivity Lack of vocal inflections
  - Alogia: Poverty of speech Thought blocking Increased latency of response
Avolition-apathy
  - Apathy: Poor grooming and hygiene Failure of appropriate role responsibilities Anergy
  - Asociality/anhedonia: Failure to engage with peers socially No interest in stimulating activities Little interest in sex Little to no intimacy with others

Treatment

Treatment Algorithm
First episode: SGA or FGA (first episode patients may respond to lower doses and be more sensitive to side effects)
No/partial response: different SGA or FGA; clozapine if suicidality, aggressive, or severe symptoms present
No/partial response: clozapine; different SGA or FGA
No/partial response: different SGA or FGA; augmentation: two antipsychotics different pharmacology, antipsychotic + ECT/rTMS, antipsychotic + mood stabilizer

Dosing
Acute illness: titrate to therapeutic doses as quickly as tolerated
- 'therapeutic' or 'equipotent' doses defined for each antipsychotic
- usually can be reached safely by 1-4 weeks
- increase doses every 2-4 weeks as outpatient; every 2-3 days as patient
- may start with BID/TID then change to QDay if possible

Maintenance: same or slightly lower dose as used in acute phase

Response Timeline

Initial response	1-2 weeks	sleep, appetite, agitation, initial positive symptom decrease	(switch warranted if no response and symptoms are very severe)
Moderate response	4-6 weeks	positive symptoms, ADLs	(except clozapine 2-3 months)
Full effects	12 weeks	negative and cognitive symptoms	

Monitoring

Baseline	BP pulse, BMI, waist circum, A1c/FPG, fasting lipid panel, AIMS/DISCUS, CMP, CBC w diff, TSH, EKG, pregnancy, drug toxicology
Every 4 mo	BP pulse, BMI, waist circum, A1c/FPG, fasting lipid panel
Every 6 mo	BP pulse, BMI, AIMS/DISCUS
Every 1 yr	every thing

Adjunct medications
Negative symptoms/Depression: maximize antipsychotic, add antidepressants as indicated
Aggression/Hostility/Mania: mood stabilizers (lithium, valproate, carbamazepine)
Anxiety: antihistamines, benzos
Insominia: antihistamines, sedating antidepressants (trazodone, mirtazapine, doxepin), hypnotics

Which antipsychotic to choose? target symptoms, PMH, FH, adherence (food, daily dosing, oral meds), cost, pharm profile/side effects, comorbitities, preference

Antipsychotic classification
1. first generation vs. second generation
   - clozapine superior, all others equally effective for positive symptoms
   - FGA more DIMD prolactin QTC
   - SGA more metabolic syndrome, additional efficacy for negative symptoms
2. potency - high, medium, low - partial agonist
3. metabolic risk - SGA>FGA - high, medium, low within the SGAs

FGA vs. SGA
- equally effective on positive symptoms if used in 'equipotent' doses (exception clozapine has superior efficacy)
- 'equipotent' doses correlates with how much it blocks D2 where >60% blockade = efficacy against positive symptoms
- SGAs can help a bit with negative symptoms
  - DA too high in mesolimbic pathway = positive symptoms (FGA+SGA block D2)
  - DA too low in mesocortical pathway = negative symptoms (SGA blocks 5HT2 which raises D2)

- high potency: drug-induced movement disorders; prolactin
- low potency: anticholinergic, sedation, hypotension

Drug-Induced Movement Disorders (DIMD)
- caused by blocking too much dopamine in nigrostriatum; post-synaptic receptors become hypersensitive
- dopamine blocking threshold >60% for efficacy >80% puts at risk for movement disorders
- risk for DIMD has to do with the potency for D2 receptor and speed of dissociation from D2 receptor
  - high potency, high risk (haloperidol, trifluoperazine, fluphenazine; risperidone, paliperidone)
  - low potency, low risk (chloropromazine, thioridazine; clozapine, olanzapine, quetiapine)
  - slow dissociation, high risk (most FGAs >> SGAs); first generation are "sticky" on receptors
  - 5HT2A protective: SGAs have less than FGAs because blocking serotonin may lessen the dopamine "overblock" and post-synaptic "sensitization"

Hyperprolactinemia
- highest risk: FGAs, risperidone, paliperidone
- dopamine disinhibition on prolactin in HPA (prolactin level >30ng/mL)
- consequences: menstrual disturbances, galactorrhea, sex dysfunction, lower testosterone, gynecomastia, infertility, decreased BMD, CV disease, breast cancer

Anticholinergic and Sedation
- anticholinergic and sedation same risk: high ACh burden/sedation with lot potency meds
- anticholinergic: M1 antagonism: blurry vision, urinary retention, dry mouth, constipation, confusion or impaired cognition, tachycardia, thermodysregulation
- sedation: H1 antagonism

Hypotension
- alpha1 antagonism: orthostasis; relevant drug interactions with antihypertensives; more frequent when patients are nonadherent
- low potency meds most common (clozapine, quietiapine, chlorpromazine) and iloperidone

Metabolic Disorders
SGAs >> FGAs
- all SGAs can cause even if "low risk" and even at "low doses"
  - H1 receptor: weight gain (>5% body weight, 1 BMI point)
  - 5HT2C, M3, H1 receptors: lipid and glucose
- FGAs can cause weight gain, may change lipid and glucose
- risk factors: treatment-naïve patients, children, family history
- major morbidity and mortality issue: puts vulnerable patients at higher risk for CV disease
- important metabolic monitoring

QTc prolongation
- normal QTc <430M <450F - prolonged QTc >450M >470F - dangerous QTc >500M or increase in >60msec above baseline
- riskiest antipsychotics: ziprasidone, iloperidone, thorazone, thoridazine (ZITT)
- risk factors: multiple drugs; female, electrolyte imbalances, cardiac disease/FH of congenital QTc, recent CVA/trauma, prolonged baseline, prior DI-QTc, >65yo

get oral trial before injectables

Clozapine
Most effective antipsychotic
- Also has the most side effects – slow titration helps with some of them
- Must weigh the side effects vs. treatment resistant psychosis

Should be offered to those with treatment nonresponse and no contraindications
- 2 adequate trials of other antipsychotics
- Suicidal or aggressive behaviors

BBB: agranulocytosis (ANC monitoring), seizures, myocarditis, OH, elderly

Highest incidence SE: metabolic changes, sedation, constipation, sialorrhea (drooling)
Lowest incidence DIMD NMS
Tobacco smoke: 1A2 inducer

REMS
Online registry to monitor for agranulocytosis
Agranulocytosis = potentially fatal drop in ANC (Pre-marketing incidence ~1.7%)
Patient, physician and pharmacy must register at www.clozapinerems.com
ANC parameters published on registry

Dispensing follows monitoring
ANC monitored: Weekly x 6 months, every 2 weeks x 6 months, monthly thereafter
Drug dispensed as: 7-, 14- or 28-day supply based on monitoring status
Must have current bloodwork within 7 days of dispensing

Skipping doses puts at risk for severe hypotension, seizures
If off for >48 hours, should re-titrate

Clozapine therapeutic trough levels
Clozapine >350ng/mL
Norclozapine also reported, is active metabolite with longer half-life
Clozapine: norclozapine ratio
Ratio < 0.5 can suggest poor adherence over the previous day or rapid metabolism of clozapine (e.g., via CYP1A2 induction)
Ratio > 3.0 could suggest that metabolic pathways are saturated or inhibited by a concomitant medication

Acute Psychosis

If unknown history, or is due to other medical or substances and NOT suspected underlying psychotic illness
- Attempt non-pharmacological de-escalation techniques if possible

If known or suspected underlying psychotic illness
- Treat with antipsychotic (re-start previous or start new)
- Second generation preferred due to preferable side effect profile
- Quickly treat to avoid harm to self or others
- Calm patient without over-sedating

First-line options for acute psychosis

haloperidol (PO 5-10mg; IM 2.5-10mg)	- often administered with lorazepam and/or diphenhydramine to provide sedation/EPS protectant effects (DPH separate)
olanzapine (ODT 5-10mg; IM 5-10mg)	- reconstitute 2.1mL SWFI, don't mix other meds syringe; do not give within 2 hours of parenteral benzo
risperidone (ODT 1-2mg)	- no short-acting injectable form available
ziprasidone (IM 10-20mg)	- reconstitute 2.1mL SWFI, don't mix other meds syringe; monitor QTc prolongation; oral not appropriate poor absorption

Movement Disorders

	Dystonia	Akathisia	Pseudoparkinsonism	Tardive Dyskinesia (TD)
Definition	Involuntary muscle contractions that cause repetitive or twisting movements. abnormal, repetitive, movements, postures	A feeling of muscle quivering, restlessness, and inability to sit still, sometimes a side effect. Most common	drug-induced movement disorder which mimics (or reveals) the s/s of idiopathic PD	late-onset and sometimes irreversible movement disorders which can include chorea, dysphonia, dystonia, tics, myoclonus
Typical time to presentation	5 days – 3 months	1st 3 months, or anytime	1st 3 months	6 months to years
Risk factors	treatment-naïve, elderly, FGAs	FGAs, aripiprazole, SSRI, TCA, lithium	women, >40yo, FGAs	middle-aged women, elderly, long-term use, FGAs, high dose, high potency
Signs/Symptoms	Acute muscle spasm, can occur in any muscle of body – look for stiffness, immobility Most frequently occur in head/neck	body restlessness Subjective/objective feelings of inner restlessness, uncomfortable and unrelenting	PD symptoms Decreased movements (mask-like face, bradykinesia, akinesia), muscle stiffness (cogwheel/ lead pipe rigidity), resting hand tremor, drooling, and shuffling gait	Involuntary movements including blinking, lip smacking, and writhing movements of the face, neck, back, trunk, and/or extremities chorea, dysphonia, dystonia, tics, myoclonus
Management	IV/IM diphenhydramine/benztropine benzatropine/DPH oral 1-2 weeks reduction of dose, slower titration, change AP	patient education reduce dose, switch AP beta-blocker, benzo	reduce dose, change AP or use oral anticholinergic (benzotropine, trihexyphenidyl, DPH, amantadine) taper anticholinergic, reassess q4-6wk	reduce dose , change AP add VMAT inhibitor (valbenazine, deut-TBZ); may be a role for clozapine or quetiapine

DIMD Management

Tardive Dyskinesia Management
VMAT2 inhibitors (40-50% reduction in AIMS scores)
valbenazine (Ingrezza): 40mg qd may increase to 80mg qd; SE: fatigue, sedation, QTc
deutetrabenzine (Austedo): 6mg qd may increase to 24mg bid; SE: NMS, depression, suicidality, agitation, QTc

Hyperprolactinemia Management (Prolactin >30ng/mL)
- MRI for prolactin tumor (rare)
- use lower dose
- switch AP (aripiprazole, quetiapine, clozapine)
- add aripiprazole; can lower prolactin levels
- wait 1-3 months for tolerance to develop
- DA agonists (bromocriptine or cabergoline) with caution

Anticholinergic Management (common with low potency AP)
Goal: reduce overall burden Manage symptoms: constipation; dry mouth (sugar free candy/gum/biotene)
Recommend getting rid of other anticholinergic medications:
- TCAs - benztropine/diphenhydramine used as prophylactic DIMD treatment - hydroxyzine - quetiapine as sleep medicine oxybutynin

Metabolic Disorders Management

Hypotension Management
- titrate slowly, emphasize adherence
- may reduce dose, take dose at bedtime, split to bid, give XR
- minimize other antihypertensives; caution sitting to standing; stay hydrated, limit EtOH

Warning about abrupt discontinuation
- various discontinuation syndromes can occur: supersensitivity psychosis, withdrawal DIMD, discomfort (like SSRI dc)

Pregnancy and Breastfeeding
- untreated psychiatric illness poses risks to baby and mother; if psychosis controlled, option to stay on current AP
- most teratogenic during 3-8 weeks gestation
- 3rd-trimester: EPS/withdrawal symptoms in newborn; low birth weight
- gestational DM (SGAs)
- no DOC (both FGA and SGA similar risks)

Learning objectives

1. Present background information regarding the epidemiology, risk factors and clinical presentation of patients with schizophrenia- spectrum disorders
2. Outline interventions for patients with schizophrenia, focusing on medication management
3. Present the usual dose, dose forms and costs of antipsychotic medications
4. Connect psychopharmacological principles with the efficacy and side effect profiles of antipsychotic medications
5. Differentiate efficacy and side effects between first and second generation antipsychotic medications
6. Present antipsychotic side effect management strategies
7. Discuss the most commonly used individual antipsychotic medications for administration, efficacy and side effect issues

Summary

Recognize which antipsychotics are a first generation vs. second generation and how that correlates with efficacy, side effects
- Clozapine is superior, all others equally effective for positive symptoms
- FGA more DIMD, prolactin, QTc prolongation
- SGA more metabolic syndrome, maybe more efficacy for negative symptoms

Recognize antipsychotics by potency and how that correlates with side effects
Recognize antipsychotics by metabolic risk category
Know how to manage all major side effects discussed as well as monitoring parameters
Know which antipsychotics absorption are affected by food
Know which antipsychotics have highest known rates of QTc prolongation
Know pharmacodynamics drug-drug interactions
Do not need to memorize doses, dose formulations or cost for exam – charts online are for future files and small groups cases

Patient is a [__ year old] [male/female] with schizophrenia. She has predominantly [positive/negative symptoms]. She has [___], her past trials of antipsychotic medications include [first/second/partial]. Other than her [positive symptoms], her bothersome symptoms include [___]. What is an appropriate choice of an antipsychotic for this patient?

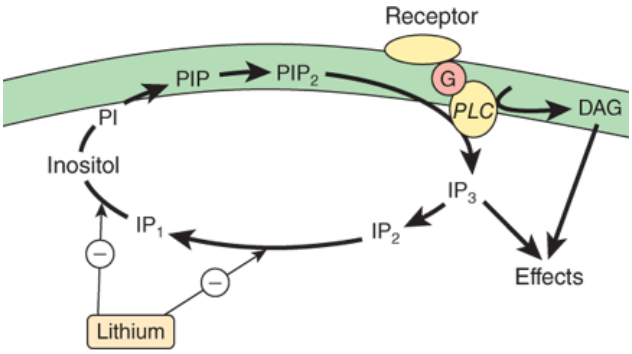
Pharmacologic therapies for Bipolar Disorder (Mood Stabilizers): Antiepileptics: valproate, carbamazepine, lamotrigine; Antipsychotics; Lithium

Lithium
- excreted by kidney
- Na sodium depletion decreases rate of excretion by increasing reabsorption of lithium by proximal tubule; increases likelihood of toxicity (renal predisposes)
- effective plasma level: 0.6 – 1.5 mM; toxicity >1.5 mM - narrow therapeutic window, must be closely monitored
- toxic effects of lithium
  - GI disturbances
  - tremor
  - renal effects: increased urination (polyuria), thurst
    - inhibition of antidiuretic hormone action by lithium; mild and transient early in therapy; monitor renal function; possible renal tubular damage
  - thyroid enlargement
  - weight gain
  - cardiac arrythmia
  - acute toxicity: confusion, motor impairment, coma, convulsions, death (3-5 mM)

MoA (unclear)
Monovalent cation (not pumped out of neuron so it accumulates in cells)
  - can mimic role of Na sodium in excitable tissues
  - can permeate voltage-sensitive Na sodium channels
Complex effects on monoamine metabolism
  - Li+ inhibits NE and DA release
Effects on inositol phosphates (most well-characterized action of Li+ so far)
  - many neurotransmitter receptors are phosphatidyl inositol (PI)-linked; linked to phospholipase C by G protein
    - alpha1-adrenergic
    - 5HT2 serotonin
    - ACh muscarinic cholinergic

Phosphatidylinositol biphosphate (PIP2) is hydrolyzed by phospholipase C to yield second messengers
  - inositol triphosphate (IP3): activates calcium release from intracellular stores
  - diacylglycerol (DAG): activates protein kinase C (PKC)

Phosphatidylinositol (PI) is synthesized from free inositol and lipid
  - Neurons (unlike other cells) cannot obtain free inositol from the plasma due to the BBB
    - Neurons recycle inositol by dephosphorylating inositol phosphates or
      newly synthesize from glucose-6-phosphate
Lithium blocks inositol phosphatases
  - Particularly inositol monophosphatase (IMPase)



Effect of lithium on the IP_3 (inositol trisphosphate) and DAG (diacylglycerol) second-messenger system. The schematic diagram shows the synaptic membrane of a neuron. (PI, inorganic phosphate; PIP_2, phosphatidylinositol-4,5-bisphosphate; PLC, phospholipase C; G, coupling protein; Effects, activation of protein kinase C, mobilization of intracellular Ca^{2+}, etc.) Lithium, by inhibiting the recycling of inositol substrates, may cause the depletion of the second-messenger source PIP_2 and therefore reduce the release of IP_3 and DAG. Lithium also acts by other mechanisms.

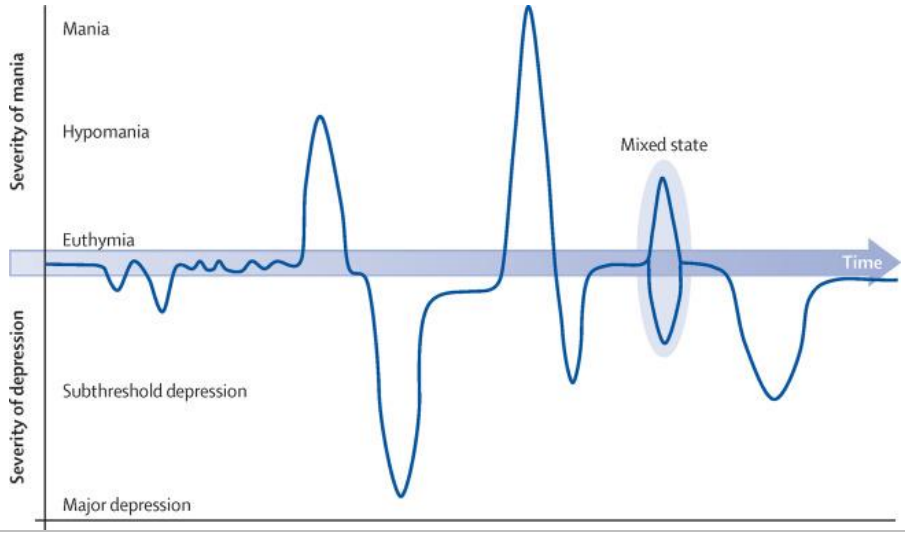
Inhibition of PI pathway by lithium
  - Blocked at point where inositol phosphate is hydrolyzed to free inositol
  - Step is required for regeneration of PI after it has been hydrolyzed by agonist action
  - Depletes membrane PI and causes accumulation of intracellular inositol phosphate
  - Results, therefore, in inhibition of agonist-stimulated IP3 formation through PI-linked receptors

<u>Summary</u>
Inhibition of inositol mono-phosphatase (IMPase) blocks neuron's ability to generate free inositol
  Diminished capacity to resynthesize PIP2 after hydrolysis in response to neurotransmitter receptor activation
Hypothesized that when firing rate of neuron is high..
  lithium-treated neurons are depleted of PIP2
    neurotransmission dependent on this messenger system is dampened
Hypothesized that effects of lithium are more evident in cells with abnormal firing rates
Target cells and receptor signalling pathways of lithium action in bipolar disorder are not completely known

Bipolar Disorder

- Recognize symptoms of bipolar mania, hypomania and depressive episodes and differentiate between bipolar I and bipolar II disorder
- Describe first and second-line treatments for acute bipolar mania and depressive episodes
- Explain the treatment goals and general principles when using PRN medications for acute agitation in bipolar mania
- Identify dosing strategies, common side effects, and required monitoring for lithium and valproic acid derivatives

euthymia: normal, tranquil mental state/mood; baseline



Manic Episode	A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting <u>at least 1 week and present most of the day, nearly every day</u>. B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present: 1. Inflated self-esteem or grandiosity. 2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep). 3. More talkative than usual or pressure to keep talking. 4. Flight of ideas or subjective experience that thoughts are racing. 5. Distractibility, as reported or observed. 6. Increase in goal-directed activity or psychomotor agitation 7. Excessive involvement in activities that have a high potential for painful consequences C. The mood disturbance is sufficiently severe to cause <u>marked impairment in social or occupational functioning or to necessitate hospitalization</u> to prevent harm to self or others, or there are psychotic features. D. The episode is not attributable to the physiological effects of a substance or another medical condition
Hypomanic Episode	A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, <u>lasting at least 4 consecutive days and present most of the day, nearly every day</u>. B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present: 1. Inflated self-esteem or grandiosity. 2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep). 3. More talkative than usual or pressure to keep talking. 4. Flight of ideas or subjective experience that thoughts are racing. 5. Distractibility, as reported or observed. 6. Increase in goal-directed activity or psychomotor agitation 7. Excessive involvement in activities that have a high potential for painful consequences C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic. D. The disturbance in mood and the change in functioning are observable by others. E. The episode is <u>not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic</u>. F. The episode is not attributable to the physiological effects of a substance or another medical condition.
Depressive Episode	A. Five (or more) of the following symptoms (nearly every day) have been present during the same <u>2-week period</u> and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. 1. Depressed mood 2. Markedly diminished interest or pleasure in activities 3. Significant unintentional weight loss or weight gain, or change in appetite 4. Insomnia or hypersomnia 5. Psychomotor agitation or retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or excessive or inappropriate guilt 8. Diminished ability to think or concentrate, or indecisiveness 9. Recurrent thoughts of death, suicidal ideation without a specific plan, or a suicide attempt or a specific plan

Bipolar I disorder	• Must have history of one manic episode • Do not need a history of depressive episode - Patients with bipolar I disorder experience manic episodes and nearly always experience major depressive and hypomanic episodes
Bipolar II disorder	• Must have a history of one hypomanic episode and at least one depressive episode • No history of a manic episode (Bipolar II diagnosis can switch to bipolar I diagnosis if patient experiences manic episode) - Bipolar II disorder is marked by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes
Bipolar disorder with psychosis	• Symptoms of psychosis are present during a mood episode • Not present outside of mood episodes

Bipolar I disorder: Hx 1 manic episode
Bipolar II disorder: Hx 1 hypomanic episode and 1 depressive episode

Comparison of DSM-5 criteria for bipolar I disorder and bipolar II disorder

	Bipolar I disorder	**Bipolar II disorder**
Manic episode(s)	Yes	No
Hypomanic episode(s)	Commonly occur, but not required	Yes
Major depressive episode(s)	Usually occur, but not required	Yes
Mixed features	May occur	May occur
Anxious distress	May occur	May occur
Rapid cycling	May occur	May occur
Psychotic features	May occur	May occur
Catatonia	May occur	May occur

Mania
- Inflated self-esteem/grandiosity
- Overactivity/decreased need for sleep
- Flight of ideas/racing thoughts
- Distractibility
- Excessive involvement in activities that have high potential for painful consequences (e.g. foolish business investments, shopping sprees, etc)
- Elevated, expansive or irritable mood for at least one week (less time if hospitalization required)
  - Must be unrelated to substance abuse or medical condition
  - Functional and social impairment also necessary
- May be related to increased catecholamine (dopamine/norepinephrine) activity; drugs that increase this activity can exacerbate mania

Risk factors: genetic (7-fold risk if first-degree relative; 50% have relative with dx); neurophysiological; psychosocial (stressful life events, trauma, abuse, anxiety)
Prevalance: 2.8% of US adults; equal genders

Clinical Course
Frequent misdx d/t presentation in depressed state; provider does not ask about episodes/pt hasn't experienced yet; delayed dx = worse outcomes (QoL, suicides)
Bipolar I late teens, Bipolar II early-mid 20s patient's spend 33% of time in depressive state; increased rate of suicide attempts (20x higher than gen pop)
Kindling effect: acceleration of episode frequency and treatment resistance with inadequate treatment

Patient evaluation
- current symptoms (depressed vs. manic episode, +/- psychosis)
- current treatment (efficacy, tolerability, adherence); past treatments
- previous mood episodes (symptoms, severity, duration, frequency, etc.)

Standardized rating scales
- *Young Mania Rating Scale (YMRS) - Bipolar Depression Rating Scale (BDRS) - Mood Disorder Questionnaire (MDQ) CGI-BP

Treatment

	Depression	Euthymia	Mania
Mood Stabilizers	antidepressant effects	maintain euthymia	antimanic effects
Antipsychotics	antidepressant effects	maintain euthymia	antimanic effects +/- antipsychotic effects
Antidepressants	antidepressant effects*		
Benzodiazepines			short-term for agitation, sleep

*antidepressants not mainstay for therapy; controversy about whether it relieves or makes symptoms worse

Acute Mania Episode

Symptoms:

- Decreased need for sleep (not tired)
- Increased goal directed activity (cleaning, working, projects etc.)
- Euphoria, irritability
- Inflated self-esteem or grandiosity (feel 'on top of the world')
- Rapid, pressured, loud speech
- Racing thoughts, flight of ideas (shifting focus frequently)
- Increased restlessness, distractibility, sexuality, physical activity
- May have hallucinations, delusions

Goals:

- Reduce agitation, impulsivity, aggression to prevent harm
- Control behaviors, restore sleep, begin resolving the mood episode

Pharmacotherapy:

First-line - lithium - valproate - SGA (olanzapine, quetiapine, aripiprazole, risperidone) - combination of above agents (not two APs)
Discontinue contributing agents: antidepressants, stimulants, steroids
Second-line - switch or combine first-line agents
Third-line - haloperidol, chlorpromazine - carbamazepine - benzos (short-term)
Treatment resistant - ECT - clozapine

Acute Agitation

Patient presentation:

- *agitation associated with mania and/or psychosis
- excessive motor activity, manifested by pacing, restless, inappropriate comments
- inappropriate sexual behaviors, cursing, verbal aggression, screaming, threatening
- aggression, physical violence, destruction of property

Goals: - Quickly treat acute agitation to prevent harm to self or others - Use the least restrictive means possible - Calm patient without over-sedating

General Principles

1. Nonpharmacologic de-escalation techniques should be attempted, if possible
2. Oral route preferred if patient is able and willing
   - Disintegrating tablets may improve adherence
   - Intramuscular (IM) may be administered if patient is unable or unwilling to take PO
3. Medications should calm patient, but not induce sleep
4. SGAs are typically preferred due to preferable side effect profile

First-line options for acute agitation

haloperidol (PO 5-10mg; IM 2.5-10mg) - often administered with lorazepam and/or diphenhydramine to provide sedation/EPS protectant effects (DPH separate)
olanzapine (ODT 5-10mg; IM 5-10mg) - reconstitute 2.1mL SWFI, don't mix other meds syringe; do not give within 2 hours of parenteral benzo (resp depression)
risperidone (ODT 1-2mg) - no short-acting injectable form available
ziprasidone (IM 10-20mg) - reconstitute 2.1mL SWFI, don't mix other meds syringe; monitor QTc prolongation; oral requires >500cal food, don't use

Acute Depressive Episode

First-line - lamotrigine - SGA (olanzapine, quetiapine, lurasidone, cariprazine)
Second-line - switch first-line agents - add lithium - lithium monotherapy

Role of Antidepressants

- Use of antidepressants in bipolar disorder is controversial; questionable benefit
  - risk for putting them into mania or hypomania

Generally not recommended, but if used:

- must be with a mood stabilizer (prevents mood from becoming manic or hypomanic)
- short-term until depressive episode resolves
- monitor closely for mood switch, increased irritability/dysphoria, lack of benefit

Maintenance Treatment

Response: 50% improvement in symptoms
Remission: absence of symptoms or minimal symptoms; return to baseline
- high risk of relapse in first 2-4 months after acute treatment - move into maintenance therapy after ~3 months of mood stability

Goals

Keep them in euthymia; prevent future mood episodes
Optimize agents and consolidate medications, if possible: monotherapy is ideal (pharmacotherapy is life-long)
First-line options

- continue agent(s) used to treat acute episode
- lithium

Lithium

Indications
- traditional “gold standard” mood stabilizer
- acute treatment of bipolar mania, hypomania, depression
- bipolar disorder maintenance treatment
- unipolar depression
- proven suicide prevention

Dosing
Initial: 600-900 mg split BID-TID
Maintenance: based on clinical response and levels
Linear (first-order) kinetics allows for predictable ratio of dose:level
- E.g. 300 mg q12 hours = trough of 0.4 then
600 mg q12 hours ≈ trough of 0.8
Once dose is known, shift to QHS dosing: renal protective effects; improved adherence
Lithium carbonate ER/IR capsules/tablet doses are interchangeable
- Lithium carbonate 300 mg = lithium citrate 8 mEq/5mL

SE: - neuro: cognitive slowing, sedation, dizziness, tremor - derm: acne, psoriasis - GI: NVD
- metabolic and endocrine: thyroid dysfunction, weight gain, edema, hyperparathyroidism, hypercalcemia - heme: benign leukocytosis
- reproductive: risk for cardiac malformations, particularly in first trimester - renal: impaired CrCl, polyuria, AKI (acute toxicity), CKD

Drug Interactions
↑lithium levels: ACE-I/ARBs, diuretics, NSAIDs, low sodium diet, dehydration, renal disease, geriatric
- NSAIDs naproxen facilitate the renal reabsorption of Li+, which can result in increased concentration above the therapeutic window which can lead to intoxication
↓lithium levels: caffeine

Monitoring
• Lithium level (12hr post-dose)
• Draw 3-5 days after initiation or dose change
• Narrow window (0.6-1.2) before toxicity
• Goal levels are approximate, treat to clinical response
• Mania ~0.8 • Depression ~0.6 • Maintenance ~0.6
• Renal function (SCr, BUN)
• Hydration status, electrolytes (consistent salt, water intake, BMP + Ca)
• Thyroid function (TSH, T3/T4)
• Pregnancy status

Patient Counseling
• Administration: take at the same time every day; take with food if it causes GI upset
• Diet: avoid large amounts of caffeine; keep salt and water intake consistent; avoid dehydration, but report sx of excessive thirst, urination
• Interactions: avoid NSAIDs; ensure all of your prescribers know you’re taking lithium

Valproic acid and derivatives

Indications: **acute** treatment of ***bipolar mania**, maintenance treatment of bipolar disorder, seizure disorders, migraine prophylaxis

Dosing: Bipolar mania

- weight-based dosing: 20-30 mg/kg/day - titrate or taper to clinical response and adequate level
- fixed dose: 500-750 mg/day - titrate by 250-500 mg every 1-3 days to clinical response and adequate level

Formulations: not all VPA formulations are equivalent; ER has 8-20% lower absorption vs. DR/IR

Valproic acid liquid (Depakene)	IR	BID-TID	
Divalproex sodium (Depakote)	DR/EC	BID-TID	
Divalproex sodium (Depakote Sprinkles)	ER	BID-TID	sprinkle on food
Divalproex sodium (Depakote ER)	ER/XL	QHS	

SE: - neuro: sedation, dizziness, ataxia, elevated ammonia, tremor - GI: NVD, anorexia - derm: rash, alopecia - heme: thrombocytopenia
- metabolic/endocrine: weight gain, edema reproductive: risk neural tube defects (category D/X) - hepatic: elevated LFTs, hepatotoxicity, pancreatitis

Monitoring

- Valproic acid total level (trough)
  - draw 3-5 days after initiation or dose change - trough range (usual) 50-100 (less clinical relevance in bipolar disorder vs. seizures)
  - once daily ER formulation (18-24 hours post-dose) - twice daily DR formulation (~12 hours post-dose)
- Hepatic function (LFTs)
- Ammonia level (if symptomatic or suspicion)
- CBC with platelets
- Pregnancy status

Teratogenicity

- No drug interaction with contraception, but particularly teratogenic

"Birth defects, decreased IQ, and neurodevelopmental disorders following in utero exposure; should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant or to treat a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable…"

- Estimated 1 in 10 babies will have a birth defect: spina bifida, facial/skull malformations, malformations of limbs, heart, kidney, urinary tract or sexual organs
- Estimated 4 in 10 babies will have developmental concerns: delayed walking, speaking, lower IQ, poor speech and language skills, memory problems, ASD

Contraception (counsel on this risk)

- avoid in females of child-bearing potential, unless on highly reliable form of contraception and all other options have been exhausted

IUD (Mirena®, Cu-IUD) Injectable (DepoProvera®) Implant (Nexplanon®) Oral contraceptives may be acceptable is strictly adherent

Lamotrigine

Indications: bipolar depression, seizure disorders

Dosing: Bipolar disorder: 25 mg daily x 2 weeks, then 50 mg daily x 2 weeks, then 100 mg daily x 1 week, then 200 mg daily; usual max is 200 mg

- adjust titration if concomitant inducers or inhibitors

SE: - neuro: dizziness, sedation, ataxia - derm: rash, SJS/TEN - GI: NVD

Monitor: LFTs, rash (no established blood levels for bipolar disorder)

SGAs

Role

- select based on mood episode
- combined with or in place of a traditional mood stabilizer
- particularly helpful in psychosis
- rapid onset of action; olanzapine has short-acting IM

Bipolar mania	- aripiprazole, olanzapine, quetiapine, risperidone, cariprazine
Bipolar depression	- olanzapine, olanzapine/fluoxetine, lurasidone, quetiapine, cariprazine
Bipolar maintenance	- continue medication from acute episode; note that LAIs exist for aripiprazole and risperidone

Bipolar Disorders Summary

- select pharmacotherapy based on current mood episode

Bipolar mania:

- monotherapy or combination
  - mood stabilizers (lithium, valproate)
  - SGAs (PO/LAI)
- short-term, acute mania
  - short-acting APs
  - benzos
  - discontinue ADTs

Bipolar depression:

- monotherapy or combination if severe symptoms
  - mood stabilizers (lamotrigine, lithium)
  - SGAs (limited)
- avoid ADTs if possible

Maintenance

- continue acute treatment (consider LAI if available)
- switch to lithium
- consolidate pharmacotherapy
- lifelong treatment

ADHD

- Explain the epidemiology/pathogenesis of ADHD - List the diagnostic criteria for ADHD - Design a therapeutic plan for ADHD treatment
- Recommend therapeutic alternatives for treatment failure - Differentiate the stimulant drugs and dosage forms
- Describe the role of non-stimulant medications - Formulate appropriate responses to parental questions about ADHD

Prevalence: 9.4% of those 2-17yo (6.1M) have been diagnosed with ADHD 6-11% kids, 3-5% adults 2-3M/1F

Etiology: unknown; genetics, enivornment, brain structure, neurochemicals
Pathophysiology

Environment: atopic disease area of interest
…

Neurochemical alterations (predominance in frontal subcortical system)
NE: attention, alertness, processing speed
DA: learning, memory, motivation, goal setting, vigilance

ADHD classification
- combined type 80% (inattentive/impulse/hyperactive) - predominantly inattentive 15% - predominantly hyperactive/impulse 5% - other unspecifed

PCPs should initiate ADHD evaluation for any 4-18yo with academic or behavioral problems and sx inattention, hyperactivity, or impulsivity

DSM-5

- **Inattention** – 6 or more symptoms persisting for 6 or more months to a degree that is maladaptive and inconsistent with developmental level AND that negatively impacts social and academic/occupational activities (**For adolescents ≥ 17 years and adults, only 5 symptoms required)**
    - Often fails to give close attention to details and makes careless mistakes
    - Often has difficulty sustaining attention
    - Often does not seem to listen when spoken to directly
    - Often does not seem to follow through on or finish tasks
    - Often has difficulty organizing tasks
    - Often avoids tasks that require sustained attention
    - Often loses things necessary for activities
    - Often is easily distracted
    - Often is forgetful in daily activities
- **Hyperactivity and Impulsivity** – 6 or more symptoms persisting for 6 or more months to a degree that is maladaptive and inconsistent with developmental level AND that negatively impacts social and academic/occupational activities (**For adolescents ≥ 17 years and adults, only 5 symptoms required)**
    - Often fidgets or restless while sitting
    - Often leaves seat
    - Often runs about or climbs excessively (may be limited to feeling restless in adolescents/adults)
    - Often has difficulty with quiet leisure activities
    - Often is “on the go” or “driven by a motor”
    - Often talks excessively
    - Often blurts out answers
    - Often has difficulty awaiting turn
    - Often interrupts or intrudes

- Several symptoms prior to age 12
- Several symptoms present in 2 or more settings (home, school, work, etc.)
- Symptoms interfere with or reduce the quality of social, academic, or occupational functioning
- Symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal)

- In partial remission
    - ADHD criteria previously met
    - Fewer than full criteria met for past 6 months
    - Symptoms still result in impairment
- Qualify if mild, moderate, or severe diagnosis

Diagnosis: DSM-5 criteria, patient interview, caregiver interview, teacher interview, ADHD symptoms scale, physical exam with neurologic status, school work/report evaluations/samples, evaluation of comorbidities
ADHD symptom scales: Conners’ Rating Scales-Revised IOWA Conners’ Teacher Rating Scale Wender Utah Rating Scale
National Initiative for Children’s Healthcare Quality (Vanderbilt Assessment Scale)

Comorbidities: anxiety, depression, tic disorders, sleep disorders, substance abuse, conduct disorder, oppositional defiant disorder, obsessive compulsive disorder, learning disabilities, autism spectrum disorder, schizophrenia, biolar disorder

Treatment
Therapeutic Goals: improve academic and social functioning, improve academics, decrease disruptive behavior, increase attention and response inhibition, improve family/teacher/peer relationships, increase independence in activities, minimize adverse effects, utilize a comprehensive approach

Options: behavior modification, pharmacologic therapy, both

Age 4-5 (preschool) 1st-line: behavioral modification 2nd-line: add methylphenidate
Age 6-11 (elementary) behavior modification + medication
Age 12-17 (adolescent) medication +/- behavioral intervention

Product selection based on efficacy, dosage form, PK and timing of pt's symptoms, cost

Stimulants
- block synaptic NE and DA reuptake
- 1st-line therapy: >70% response rate
- comparable efficacy among stimulant agents: 3 mo trial of dose titration; <6yo failing behavioral therapy add methylphenidate (preferred, off-label)
- heterogeneous response
  - not correlated to serum levels
  - slight variations in NE and DA effects between products and patients
    - methylphenidate/dexmethylphenidate block DA reuptake from the synaptic cleft into the presynaptic neuron via DA transporter protein
    - amphetamine enhances release of NE and DA from storage vesicles in the presynaptic neuron and blocks storage and reuptake from the presynaptic cleft
    - monoamine oxidase (MAO) inhibition: amphetamines > methylphenidate

Medications: methylphenidate, dexmethylphenidate, dextroamphetamine, mixed amphetamine salts, amphetamine (dextro+levo), lisdexamfetamine

Pharmacokinetics
short-acting (IR)
- onset <1hr
- duration 3-6hr
- multiple daily doses
- peak related efficacy (rapid attainment of peak)
- behavioral rebound (rapid drop from peak)

intermediate-acting (SR, ER)
- wax-matrix or hydrophilic polymer controlled release mechanism
- reduced side effects due to smaller peak to trough difference
- delayed onset, so less optimal early AM coverage
- slightly longer duration (3-8 hours), but not sufficient for full school day coverage
- not as efficacious as IR preparations
- do not chew

long-acting
- onset 1 to 3 hours
- duration 10 to 12 hours
- mixed IR and controlled release beads - (Metadate CD, Ritalin LA, Aptensio XR, Adderall XR, Focalin XR, Mydayis); may sprinkle beads, but do not chew
- osmotic release (Concerta); cannot be ground up & snorted, ghost tablets
- ion exchange resin (sodium polystyrene sulfonate) with polymer coating - (Quillivant XR, QuilliChew ER, Cotempla XR-ODT, Adzenys XR-ODT, Dyanavel XR)
- high-fat meals delay absorption of IR component

long-acting, delayed-release (Jornay PM)
- delayed-release film coating releases drug 12 hours after administration (dosed at bedtime)
- peak at 14 hours after administration - extended release throughout rest of the day - may open capsule and sprinkle on applesauce

transdermal patch (Daytrana)
- day-long control 2-12 hours post-application to hip (apply 2 hours prior to desired effect) with 9 hour wear time (flexible)
- dot matrix composition (bigger patch bigger dose) - dose is patch size and time dependent

lisdexamfetamine dimesylate (Vyvanse)
- prodrug converted to dextroamphetamine and L-lysine via saturatable first-pass intestinal and/or hepatic metabolism
- slightly delayed onset of action (2 hours)
- capsules may be opened and contents dissolved in a glass of water

Stimulant Dosing

IR formulations
- Start with lowest available dose given in AM or BID
- Titrate weekly
  - Add Noon dose
  - Increase AM &/or Noon dose
  - Add 4PM dose

ER/SR formulations
- Start with lowest available dose given in AM
- More difficult to titrate
  - Increase AM dose
  - Add IR dose in AM or 4PM

Long-acting formulations
- Start with lowest available dose given in AM
- Titrate weekly
- May need 2 different formulations
- May still need school-time or PM dosing (adolescents)
- New practice standard

Maximum doses: Methylphenidate: 60-72 mg (100 mg?) Dexmethylphenidate: 20 (IR), 40 mg (XR)
Dextroamphetamine: 40-60 mg Mixed amphetamine salts: 30-60 mg Lisdexamfetamine: 70 mg

Patch

Titration regarding Daytrana patch: Week1: 10mg/9hr=1.1mg/hr=12cm^2 Week2: 15mg=1.6=18.75 Week3: 20mg=2.2=25 Week4: 30mg=3.3=37.5
- if patch does not fully adhere or is partially/fully detached during wear time, the patch should be discarded and a new patch replaced to complete wear time
- do not apply or re-apply with dressings, tape, or other common adhesives - exposure to water during bathing, swimming, or showering can affect patch adherence
- do not apply hydrocortisone or other topicals immediately prior to patch application; potential ADEs and effects on patch adhesion; methylphenidate absorption are unknown
- do not cut patches - avoid exposure to external heat sources (2x absorption) - may cause permanent hypopigmentation (chemical leukoderma)

Stimulant precaution: Sudden death/serious CV events in patients with preexisting structural abnormalities or other serious heart problems
- caution: seizure disorders, tics/Tourette's syndrome (7% ADHD have tics/Tourette's; 60% of Tourette's have ADHD); DM, bipolar or psychiatric disorders
- avoid use in severe HTN or CVD, hyperthyroidism, severe anxiety, previous illicit/stimulant drug abuse

Stimulant Side Effects

Common: Insomnia Anorexia/weight loss Growth suppression Headache Nausea Irritability/jitteriness Rebound symptoms
Uncommon: Tics Sadness/dysphoria (preschool more common) Zombie-like state Hallucinations Tachycardia Hypertension

Side Effect Management
- dose reduction
- frequency/timing adjustments
- change to alternative formulation or stimulant; adjunct agents
- sleep hygiene
- nutritional adjustments
- "Drug Holiday": decrease/stop dosing during summer break, school holidays, weekends; catch-up growth

Questions

Will my child grow up short?
- appetite suppression can occur; patients usually "catch up" in adolescence; if growth slows may consider 'drug holiday' to allow catch up during summer
- alert physician if child has CF, short gut syndrome, other GI conditions - 1-2cm shorter predicted, lifetime dose exposure dependent

Will my child have a heart attack?
- can occur if hx cardiac problems (congential heart disease, HTN, arrhythmias); alert physician if FH for SCD or early MI
- not typically concern in healthy: ↑BP 1-4mmHg, ↑HR 2-3bpm; 5-15% will have clinically significant changes - monitor BP/pulse - ECG prn

Will my child become and addict?
- addictive properties are minimal if appropriately used for patients with ADHD; abuse higher with untreated ADHD patients
- alert if psychosocial situation is ripe for diversion or abuse (use of Concerta, Vyvanse, nonstimulants)
- drug diversion: 14M monthly Rx in 2011 for 20-39yo (2.5x increase in 4 years)

Will Strattera make my teen suicidal?
- small potential risk esp in pt with depressive/psychiatric sx; adolescents are highest risk for suicide; closely monitor worsening/behavioral change during intiation

Ritalin LA or Metadate CD	methylphenidate ER		10 mg	20 mg	30 mg	40 mg	50 mg	60 mg
Concerta	methylphenidate ER			18 mg	36 mg	54 mg	72 mg	
Focalin XR	dexmethylphenidate		5 mg	10 mg	15 mg	20 mg	25 mg	30 mg
Adderall XR	dextroamphetamine/ amphetamine ER		5 mg	10 mg	15 mg	20 mg	25 mg	30 mg
Vyvanse	lisdexamfetamine	10 mg	20 mg	30 mg	40 mg	50 mg	60mg	70 mg

Nonstimulants

atomextine (Strattera)
- nonstimulant selective presynaptic NE reuptake inhibitor; increases DA in prefrontal cortex but not in striatum or nucleus accumbens; less abuse potential/tics
- inferior efficacy; 70% efficacy; continuous symptoms relief - 2nd-line therapy; lacks long-term efficacy studies, occasional combo if rebound
- 2-4 weeks for onset of effect (up to 6-8 weeks for max) - 2D6 metabolism (PM metabolizers, longer half life, require dose cut)
- dosing: children <70kg: 0.5mg/kg/d for 3 days, titrate to target 1.2mg/kg/d (max 1.4mg/kg/d or 100mg/d); single AM dose or divided twice daily
- dosing: adult >70kg: 25-40mg/day for 3 days, titrate to target 80mg/d (max 100mg/d); qd or bid
- precautions: suicidal ideation, hepatotoxicity, CV risk, depression
- SE: abd pain, NV, dec appetite, const, dry mouth, dizz, sex dysfunction, mood swings, growth suppression

When to consider: lack of abuse potential; may be preferred for tics, anxiety, substance abuse; stimulant intolerance (anorexia) or failure

α2-adrenergic agonists

monotherapy: guanfacine ER (Intuniv), clonidine ER (Kapvay) adjunctive: guanfacine IR/ER, clonidine IR/ER/patch
- inhibit NE release presynaptically; stimulate postsynaptic α2-subtype of NE receptors in prefrontal and locus coeruleus, increasing blood flow
- inferior effectiveness; niche uses - 3A4 substrate, lots of DI 1-4mg/day
  - monotherapy with concomitant tic disorder and/or oppositional conditions (anger, aggression, disruptive behavior, hostility, irritability)
  - adjunctive use for oppositional conditions
  - adjunctive use with partial stimulant response
  - adjunctive use for side effect management (sleep)
- SE: sedation (guanfacine less), dizziness (guanfacine less), hypotension, syncope, bradycardia, nausea, constipation
- CV risk may be increased when used with stimulants → baseline ECG with BP monitoring (see AHA statement)
  rebound HTN if suddenly d/c'd (unless low-dose at bedtime)
- CI: depression, syncope, dehydration
- dosing ER: guanfacine ER 1mg qd, titrate 1-2 weeks (max 4mg/d) clonidine ER 0.1mg qhs, titrate 1-2 weeks max 0.4mg/d, use bid after first titration
- dosing IR: guanfacine 0.5mg qhs (max 5mg/d), titrate 1-2 weeks clonidine 0.05mg qhs (max 0.4mg/d), start low titrate 1-2 weeks

bupropion
- NE and DA reuptake inhibitor; monocyclic antidepressant, structurally similar to amphetamine, better than TCAs, less effective than stimulants (weak inhibitor)
- niche: ADHD with depression
- SE: weight loss, NV, HA, insominia, agitation, fatigue, dry mouth, rash, tremor, suicidality; anorexia less common; CV risk, aggravates tics
- CI: bulimia nervosa, seizures
- dosing: 3mg/kg/day (150mg/d adults), titrated weekly to 6mg/kg/d (max 450mg/d) SR q12h or XL q24h

TCAs
- block NE and serotonin at the presynaptic transporter site; less effective than stimulants; desipramine, imipramine (preferred)
- reduce hyperactivity and improve mood and sleep; not affect concetration 4 weeks until clinical response
- niche: ADHD with depression or anxiety
- precautions: CV risks, anticholinergic side effects, suicidality, withdrawal, overdose ECG monitoring

venlafaxine
- selective inhibitor of NE and 5HT reuptake and weak DA reuptake inhibitor; limited ADHD data
- niche: ADHD with depression or anxiety
- SE: somnolence, HA, N, suicidality

complementary/alternative medicine
- omega-3 fatty acids (EPA/DHA); external trigeminal nerve stimulation (eTNS)
- elimination diets (oligoantigenic diets), mineral supplements (zinc, iron, magnesium); CBD oil, Herbal products, EEG biofeedback
- EndeavorRx: FDA-approved digital therapeutic device (video game); $450 for 3mo prescription through online pharmacy
  - age 8-12yo with primarily inattentive or combined type ADHD; adaptive sensory stimuli and simultaneous motor challenges

Product Selection: efficacy, dosage form, PK and timing of patient's symptoms, cost

ADHD treatment failure
- reevaluate symptoms and side effects
  - change to longer acting or shorter acting formulation; change to alternative stimulant; change to nonstimulant; add adjunctive agent
- consider alternative diagnosis

Analgesics

Pathophysiology

Introduction

physiologic and protective (adaptive) afferent to CNS efferent from CNS to organs
pathophysiologic and harmful (maladaptive)

somatic: permits localization of pain—discriminates among different kinds of painful sensation (location, burning, stinging, describe qualities)
affective: - activates circuits in brain that produce negative emotion (brain stem systems increase arousal; hypothalamous and amygdala that initiate fear/stress)
- suppresses behaviors that are antisurvival (interrupts ongoing behavior/demands attention; can produce suffering and disability when chronic)

Overview of Nociceptive Circuit: Activation of the peripheral terminal by a noxious stimulus leads to the generation of action potentials, which are conducted to the dorsal horn of the spinal cord. Neurotransmission in dorsal horn relays signal to CNS neurons, which send signal to brain. This circuit is also subject to descending modulatory control.

Primary nociceptive neurons must distinguish between noxious and innocuous stimuli; generally small diameter axons, slower conduction speed; high threshold for stimulation or are capable of coding the intensity of the stimulus (by frequency of impulses relayed to brain)
A_δ fibers: thinly mylenated conduction speed 20m/s - respond mostly to noxious mechanical stimuli or thermal heat
C fibers: unmylenated, slower conduction speed - higher threshold, respond nonselectively (mechanical, thermal, chemical); aka 'polymodal nociceptors'

Nerve damage can lead to neuropathic pain (stroke, MS, DM neuropathy, infection, cancer, amputation, HIV, trigeminal neuralgia)
- stimulation of A_δ and C fibers results in excitatory transmission in dorsal horn neurons
- triggers NMDA (glutamate receptors) which are excitatory; long-lasting increases in excitability of dorsal horn neurons

Opioid Signaling

Endogenous opioid receptor agonists
- start as large precursor proteins, cleaved to form neuropeptide neurotransmitters

preproopiomelanocortin (POMC) → β-endorphin
preproenkephalin → Met/Leu-enkephalin
preprodynorphin → dynorphin

Endogenous Opioid Peptides all have same 4 aa N-terminus

		μ	δ	κ
Met-enkephalin	**Tyr-Gly-Gly-Phe-Met**	++	+++	
Leu-enkephalin	**Tyr-Gly-Gly-Phe-Leu**	++	+++	
β-Endorphin	**Tyr-Gly-Gly-Phe-Met**—	+++	+++	
Dynorphin A	**Tyr-Gly-Gly-Phe-Leu**—	++		+++
Dynorphin B	**Tyr-Gly-Gly-Phe-Leu**—	+	+	+++
α-Neoendorphin	**Tyr-Gly-Gly-Phe-Leu**—	+	+	+++
Endomorphin 1	Tyr-Pro-Trp-Phe-NH_2	+++		

Opioid receptors- all G protein coupled metabotropic μ (mu) κ (kappa) δ (delta)
- $G_{i/0}$ type (inhibitory G protein)
  - when activated, facilitates opening of K+ (K+ leaves cell, hyperpolarization) and closing of Ca++ channels
  - K+ channels important for setting resting membrane potential
    - so increasing K+ channel conductance, stabilize membrane potential and make it less likely to fire AP = inhibitory to neuronal activation
  - Ca++ channels important for neurotransmitter release
    - so reducing activation of Ca++ channels would reduce neurotransmitter release
  - inhibit adenylate cyclase and decrease cAMP
- though opioid receptors are not ion channels, they can indirectly effect activity of other ion channels
  - coupled to inhibitory G protein, would ultimately modulate through series of events
    - K+ activation would stabilize membrane potential, reduce AP generation and then facilitation closing of Ca++ channels, reducing neurotransmitter release

μ (mu) supraspinal (brain) and spinal analgesia; slowed GI transit euphoria sedation inhibition of respiration tolerance/dependence
δ (delta) supraspinal (brain) and spinal analgesia
κ (kappa) supraspinal (brain) and spinal analgesia; slowed GI transit psychotomimetic effects (dysphoria/negative emotional effect)

Ascending pathway A afferent nociceptor (periphery) B dorsal horn (spinal cord) C ventral caudal thalamus (cortex)
Descending pathway A periaqueductal (midbrain) B rostral ventral medulla (medulla/pons) C dorsal horn (spinal cord)

Opioid Drugs

<u>opioid agonist</u>

morphine → morphine-3-glucuronide: inactive metabolite with neuroexcitatory properties
morphine → morphine-6-glucuronide: active metabolite; more potent than parent drug
methadone: also a glutamate receptor antagonist (NMDA subtype); use in neuropathic pain and narcotic addiction in detox/maintenance programs
fentanyl: lipophilic; rapid and short-acting
oxycodone
hydrocodone
codeine
tramadol: metabolite specific for mu receptors (weak); chemically unrelated to other opioids; also inhibits 5HT and NE reuptake

<u>mixed agonist-antagonist</u>

- in contrast to mu agonists, kappa agonists can be aversive (negative emotional effects)
- partial mu agonists can displace full agonist

pentazocine (Talwin): partial mu agonist + kappa agonist
butorphanol (Stadol: partial mu agonist + kappa agonist
buprenorphine (Buprenex): partial mu agonist (+possible kappa antagonist)
nalbuphine (Nubain): mu antagonist and can precipitate withdrawal in dependent patients + kappa agonist

Pharmacological Actions of Opioids

• analgesia: reduction in sensation of pain; reduces effective component of pain; may be action in limbic system (emotional regulation); related to euphoric effect?
• euphoria: powerful sense of contentment and wellbeing; reduce anxiety/agitation; sudden rush when IV
  - thought to be mediated by mu receptors; may be balanced by dysphoria caused by kappa receptors; opioids vary in euphoria depending on receptor subtype
• respiratory depression: mediated by mu receptors; decrease in sensitivity to carbon dioxide; occurs at normal doses
• GI tract: increases tone and reduces motility = constipation; mediated by effect on local nerves as well as some central action
• pupillary construction: centrally mediated stimulation of oculomotor nucleus; pinpoint pupils (miosis) diagnostic feature of overdose
• N/V: activation of chemoreceptor trigger zone
• suppresion of cough reflex
• Tolerance: increase in dose needed to produce pharmacological effect
  - minimal tolerance to GI effects (constipation), miosis, convulsions
• Dependence: physical and psychological; physiologic withdrawal syndrome, craving
  - abstinence syndrome is the abrupt withdrawal leads to increased irritability, loss of weight, shaking, flu-like symptoms, insomnia

<u>opioid antagonist</u>

naloxone (Narcan): used alone to reverse acute opioid overdose; combined with partial agonist buprenorphine (Suboxone) for opioid dependence
naltrexone (Vivitrol): maintenance treatment to prevent relapse in opioid use disorder; prevents user from experiencing opioid intoxication or physiologic dependence with subsequent use; thus reinforces abstinence; also used to treat alcohol dependence (role of endogenous opioids in alcohol dependence?)
naloxegol (Movantik): naloxone conjugated with polyethylene glycol polymer, limits ability to penetrate BBB; indication: opioid-induced constipation
methylnaltrexone (Relistor): quarternary amine derivative of naltrexone with limited ability to penetrate CNS; indication: opioid-induced constipation

Opioid Use Disorder

- acute withdrawal - maintenance during long-term psychosocial therapy; taper off to help withdrawal symptoms and beginning of addiction therapy

methadone (full mu agonist = greater danger of overdose)
buprenorphine (partial mu agonist = safer in overdose, but can precipitate withdrawal from full agonist)
naltrexone: for motivated abstinent (complete withdrawal) patients can be used to prevent relapse (blocks intoxicating effects of opioid use); LAI qmo available

<u>Sensitization</u>

- exaggerated response leads to protection of injured area

• Diffusible chemical mediators that modulate excitation of nociceptive neuron terminals
  - Sensitize nociceptive neurons to subsequent stimulation
  - Example: arachidonic acid metabolites such as prostaglandins
  - Usually extends beyond borders of tissue damage and decrease threshold for firing
  - Often previously unpainful stimuli become painful; Also known as 'allodynia
• Nociceptive neurons express many receptors
  - Permits response to wide range of mediators
  - Tissue damage causes release of Ions (including increased H+(acidification)), ATP, Serotonin (from platelets), Histamine (from mast cells), Bradykinin

Sensitizing mediators

  - prostaglandins released from damaged tissues, increase sensitization so next time bradykinin comes along bigger response and pain sensation
  - bradykinin activates nociceptive neurons directly and can also sensitize indirectly by stimulating synthesis of prostaglandins
  - free nerve endings may release substances that activate adjacent nociceptive neurons and contribute to pain/inflammation
    - substance P: causes valsodilation, contributes to edema; aids generation of bradykinin from kininogen; release histamine from mast cells; receptor NK1
    - CGRP (calcitonin gene related peptide)

injury → release of PG BK K 5HT → persist activation/sensitization of Aδ/C → activity in ascending pathways+spinal facilitation → exaggerated output (hyperalgesia and ongoing pain)

NSAIDs
COX: first enzyme in pathway that generates prostaglandins from precursor arachidonic acid
- COX1: expressed in most tissue
- COX2: important target for antiinflam and analgesic; induced in tissues and inflammatory cells in response to inflamed and pain
unwanted effects: ulceration of gastric duodenal mucosa due to inhibition of COX1
most are nonselective; development of COX2-selective (celecoxib)

zoconitide (Prialt)
- intrathecal spinal infusion, neuropathic pain - cone snail venom; peptide
- blocks presynaptic N-type calcium channels; decrease excitatory neurotransmitter release; psychiatric side effects

Local anesthetics
lidocaine, benzocaine, etc. - used to cause nerve block; epinephrine as vasoconstrictor to reduce blood flow at injection site
- act to block sodium channel function; use-dependent blockers; bind strongly to inactivated state of sodiumchannel
- activity is pH dependent: increased at alkaline pH, lower proportion of ionized molecules; drug crosses nerve sheath and axon membrane to reach INNER side cystoplasmic of sodium channel; ionized form not very permeable at acid pH; inflamed tissues can be acidic and resistant to anesthesia

capsaicin
- alkaloid derived from Solanaceae family plan (hot chilly peppers)
- activator of transient resceptor potential vanilloid (TRPV1) receptor on c-fiber sensory neurons; TRPV1 ligand-gated nonselective cation channel
analgesic action: stimulates then desensitizes the TRPV1 channel to capsaicin and other noxious stimuli; causes local depletion of substance P

Migraine
see notes

triptans: serotonin 1B/1D receptor agonists; located on intracranial blood vessels leads to vasoconstriction relief of migraine headache; or inh proinflam nt release
- metabotropic receptor decreases cAMP
- constrict large cranial vessles
- inhibits trigeminal nerve terminals (presyn autoreceptors/modulate nt release)
- inhibit pain transmission

Pain Management

1. Given patient specific data, identify the pain type and develop appropriate goals for the patient's pain
2. Identify key characteristics for non-opioid and opioid medications utilized in pain management
3. Select the most appropriate pain medication therapy based on specific patient data
4. Distinguish a true allergic reaction from side effects caused by opioids based upon patient information
5. Recommend a treatment plan for common side effects caused by opioids
6. Develop an appropriate monitoring plan based on a specific medication therapy (think safety and efficacy)
7. Compare and contrast advantages and disadvantages of methadone therapy
8. Adjust a patient's medication treatment plan based upon given information

https://accesspharmacy-mhmedical-com.proxy.lib.ohio-state.edu/content.aspx?bookid=2577&sectionid=226724502

Pain Management Goals

• Maximize the patient's health related quality of life:

– Decrease pain intensity – Maintain level of functioning – Minimize physical deterioration – Improve family/social relationships – Minimize dependency

Classifications of Drugs to Treat Pain

non-opioids: APAP, ASA, NSAIDs, tramadol

mild-mod opioids: hydrocodone/APAP, oxydodone/APAP

mod-severe: morphine, oxycodone, hydromorphone, oxymorphone, fentanyl, methadone

(codeine/APAP not commonly recommended for pain)

Modified WHO Pain Ladder

Step 1: non-opioids +/- adjuvant:

Step 2: mild-mod opioids +/- non-opioid adjuvant

Step 3: mod-severe opioids +/- non-opioids +/- adjuvant

Proper Pain Assessment – PQRSTU

Provoking/pallative factors Quality Region/Radiate Severity/intensity Temporal/Time (onset, duration, freq) U (you the patient)

- onset, location, duration, aggravation, alleviating, radiation, severity, quality insomnia, relationships, anxiety, ADLs

Pain Scales give a false sense of security

Types of pain: nociceptive (pain in response to noxious stimuli; somatic or visceral); neuropathic (pain in response to nerve damage/dysfunction in nervous system)

Patient considerations:

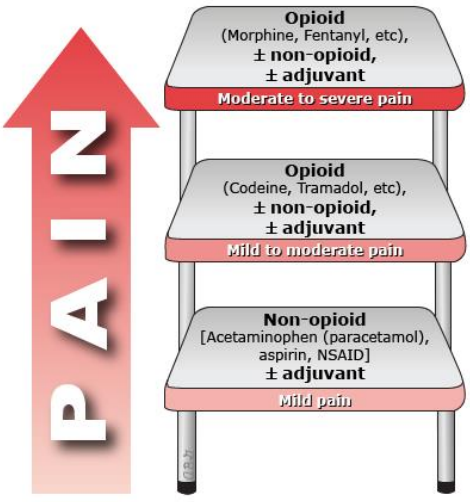
- clinical factors—state of patient (age, condition acute vs. chronic, malignant vs. nonmalignant, comorbidities)
- PK

Pharmacological consideraitons:

- onset of action
- peak effect
- duration of action
- half-life
- side effect profile

Simplified Pain Decision Tree

- Pain
  - Exisential pain
  - Physical pain
    - malignant
    - non-malignant
      - neuropathic pain (shooting, burning, tingling)
      - nociceptive pain (dull, achy)
        - chronic (3-6mo)
        - acute
          - mild
          - moderate
          - severe



Nonpharm/interventional pain management

- surgical (cordotomy) - anesthetic (nerve block) - physical therapy (exercise, heat, cold) - neurostimulation (TENS, acupuncture)
- psychological approach (biofeedback, cognitive (relaxation, imagery, hypnonsis), behavior therapy, psychotherapy) - complementary (massage art music aroma)

Non-Opioid Analgesics

acetaminophen

- step 1 analgesic, co-analgesic; utilized for mild-moderate pain, headache, fever - monotherapy and add-on with opioids (synergistic)
- onset 30min - DOA 4hrs (ER longer) - well tolerated, minimal SE - max dose is 3-3.25g; hepatic toxicity >4g/24hr

IV: Orifmev (expensive, inject slowly over 15min, monotherapy mild-mod or adjunct to opioids in mod-severe)

NSAIDs

- step 1 analgesic, coanalgesic; used for bone, inflammatory pain, fever
- all have **analgesic ceiling effects**; individual variation, serial trials - higher doses for inflammation than pain (ibu pain 200-400mg; antiinflam 600-800mg)
- inhibit COX, varying COX-2 selectivity
  - COX-1 selective: ibuprofen, naproxen, aspirin, indomethacin, ketorolac (IV hospital; max 5 day use)
  - COX-2 selective: 5-fold: diclofenac 5-50 fold: meloxicam celecoxib etodolac >50-fold rofecoxib

ADEs: very high incidence of adverse events

- gastropathy: gastric cytoprotection if appropriate; COX-2 selective less irritating (ASA diminishes effect)
- renal insufficiency: maintain adequate hydration - stop NSAID for safety (low platelet, elevated INR, AST/ALT)
- effect on platelet aggregation: assess for coagulotherapy
- cardiac: conflicting data; short-term use of NSAIDs in patients with preexisting heart disease increases risk for MI/death (except ASA)
  - NSAIDs are most common cause of drug-induced CHF exacerbations in geriatric patients

tramadol

- used for mild-mod pain; second/third-line for neuropathic pain - caution patients risked for seizures - careful brain metastases, head trauma
- primary action central activity - prodrug; secondary action very weak mu1 receptor activity

tapentadol (Nucynta, ER)

- approved for mod-severe acute pain; not rec'd severe renal/liver; slightly less ADEs than traditional opioids
- classified as opioid, CII - inhibits NE reuptake - stronger at mu receptor than tramadol; but not as much as pure opioids

Opioids

MoA: modify both sensory and affective aspects of pain

- inhibit transmission of input from periphery to spinal cord; also activates descending inhibitory pathways that modulate transmission in the spinal cord

Combination products

- effective for mild-moderate nociceptive pain (visceral and somatic)
- only IR products: hydrocodone/APAP, oxycodone/APAP, codeine/APAP**

Pure products

- effective for moderate-severe pain
- IR and ER: morpine, oxycodone, hydromorphone, oxymorphone, fentantyl, methadone

IR dosing, acute pain

- dose q4h for round the clock coverage (exception fentanyl, methadone, buprenorphine)
- dose q4h prn for intermittent pain
- adjust dose daily
  - mild-mod pain ↑25-50%
  - severe/uncontrolled ↑50-100% (adjust more quickly for severe uncontrolled pain)

ER dosing

- "for the management of pain severe enough to require daily, around-the-clock opioid treatment for which alternative treatments are inadequate"
- benefits?
- dose q8h, q12h, q24h (product specific); don't crush/chew, may flush time-release granules down feeding tubes
- adjust q2-3 days (once steady-state reached)

Chemical classes of opioids

- phenanthrenes (derived from opium): morphine, codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone
- phenylpiperidine derivative: mpeiridine, fentanyl
- diphenylheptane derivative: methadone

If true allergy (anaphylactic, difficulty breathing, tongue/lips/face swelling, hives, etc) don't use same class.

morphine

- WHO DOC - multiple dosage forms - cost effect
- morphine is our opioid of choice for either acute or chronic, moderate to severe, nociceptive pain
- M6G active hangs around longer than morphine - M3G can cause hyperalgesia or hyperallodynia

avoid: morphine-3 glucuronide (M3G): myclonus, neuroexcitatory allodynia, accumulates in patients with renal failure and higher doses (>300mg/day)

oxycodone

use over morphine: renal failure in chronic pain, high dose opioid needs, side effects from morphine
available in oral formulations (ER expensive)

hydromorphone

use over morphine: high dose opioid needs, side effects from morphine
available oral and parenteral (ER is Exalgo)
caution in renal failure: metabolism similar to morphine

oxymorphone
use over morphine: high dose opioid needs, side effects from morphine; does not induce or inhibit 2C9 or 3A4, educate about adverse effects of infecting tablets
available IR ER

codeine
- only effective for mild-moderate pain - prodrug, metabolized to morphine in liver - natural opiate (more side effects)
- very high incidence of constipation and NV
- available as pure or in combo T1 T2 T3 T4

hydrocodone
- effective for mild-moderate pain when combined with APAP
- available as pure (Hysingla, Zohydro) or combo (Vicodin, Norco)

meperidine
- only effective for mild-moderate pain - not routinely recommended - poor oral absorption
- normeperidine toxic metabolite (HL 6hr, no analgesia; psychotomimetic ADEs, myoclonus, seizures; accumulates with renal failure)

fentanyl
- very lipophilic (crosses mucus membranes) - very quick onset and duration of action - 3A4 heavily metabolized
- available in IV/SC
  - transmucosal (cancer BTP in opiod tolerant patient (morphine >60mg >2weeks); several products not interchangeable
  - transdermal patch (Duragesic, slow onset, difficult to dose and titrate); benefits compliance, unable to take PO/PR/SL, opioid abuse/diversion

methadone
- superior pain relief
- properties: lipophilic, well absorbed; rapid onset (30-60min); inhibits 5HT NE reuptake; NMDA antagonist
- multiple DDI, QTc, difficult to dose; long/variable elim HL (4-130hr); duration of effect shorter than elimination phase HL
consider use: neuropathic pain, renal insufficiency, pain that's difficult to manage (rapidly escalating doses); intolerant SE; consider consult before using
patient selection: high risk of cardiac arrhythmias, severe hepatic impairment; evaluate compliance, intended effects

Mixed agonist-antagonists
- pentazocine (Talwin), butorphanol (Stadol)
- not routinely recommended; ceiling effect
- compete with agonists →withdrawal
- analgesic ceiling effect
- high risk of psychotomimetic adverse effects

buprenorphine
- considered partial mu-agonist at formulations approved for pain: patches (Butrans): 5, 10, 20 mcg/hr; apply once weekly mod-severe transmucosal (Belbuca)
- lower doses, behaves as full mu-agonist
- binds receptors very tightly; higher doses used for addiction, blocks opioid agonists
- if someone on Butrans patch for pain, can still use full-mu agonist for BTP because not going to be enough buprenorphine at receptor to block all receptors

Choosing opioid in organ failure
Hepatic (avoid codeine, hydrocodone, tramadol)
  1st: hydromorphone, methadone, morphine, oxymorphone (?)
  2nd: oxycodone, fentanyl, buprenorphine (?)
Renal (avoid morphine, codeine, tramadol)
  1st: methadone, fentanyl, oxycodone, oxymorphone, buprenorphine
  2nd: hydromorphone, hydrocodone

Opioid Adverse Effects
common: constipation (80%), dry mouth, N/V (15/20%), sedation, pruritus (2-10%)
uncommon: bad dreams/hallucinations, dysphoria/delirium, myoclonus/seizures, urinary retention, respiratory depression

Constipation
- common to all opioids; effects myenteric plexus of gut; easier to prevent than treat; tolerance does not develop to constipation; dietary alone insufficient
First-line: Senna +/- docusate sodium (stimulant laxative +/- softener)
Osmotic Carthartic: requires adequate hydration - milf of magnesia - lactulose - PEG3350 (Miralax)
Others: prokineteic agents selective opioid antagonist: naloxegol (Movantik), methylnaltrexone (Relistor) lubiprostone bulk forming agents (avoid debilit)

N/V
- occurs with irritation or increase dose; caused by stimulation of receptors in brain and decreased GI motility;
- try decreasing dose or changing route of administration; alternative opioid if refractory
Antiemetics for treatment/prevention (DA-blocking)
- prochlorperazine 10mg q6h - haloperidol 0.5-1mg q6-12h (palliative) - metoclopramide* 10mg q6h - promethazine 12.5-25mg q6h (sedating)
Second-line considerations: serotonin antagonists, anticholinergics

Pruritus
- possibly related to mast cell destabilization; morphine, hydromorphone; challenging to manage; possibly related to central mechanism (serotonin)
Treatment: 1. opioid rotation 2. antihistamines 3. 5HT3 antagonists 4. Others (topical emollient Sarna Lotion)

Sedation
- can lead to noncompliance and decreased QoL; partially related to anticholinergic activity; seen primarily in opioid naïve patients and initiation/increase dose
Treatment: distinguish from exhaustion due to pain; avoid other sedating meds; reduce dose, alternative opioid or route

Respiratory depression
as you increase dose: pain .. analgesia .. sedation .. loss of consciousness .. respiratory depression
- pain is a potent stimulus to breathe; loss of consciousness precedes repiratory depression; pharmacologic tolerance is rapid
management: identify high risk: opioid naïve patients (young and old), COPD, obese, recent abdominal surgery
- if stable, treat contributing causes: reduce opioid dose and monitor
- if unstable vitals, pinpoint pupils: naloxone 1mg IV q1-2min

ADEs chronic opioid use
- hormonal imbalance: decrease testosterone/estrogen leading to decreased libido and energy; small increased risk of osteoporosis
- immune suppression: several opioids associated with immunosuppressive properties

Opioid allergy
- NV, constipation, drowsy, confusion = adverse effects, not allergic reactions
- anaphylactic reactions are only true allergies where incidence 1:200,000
- uticaria, bronchospasm can be allergies; need careful assessment

Opioid Conversions

Step 1: identify both current and desired drug, dose, route, interval
Step 2: determine amount of current total daily drug dose in 24 hours
Step 3: set up ratio to determine amount of desired drug/24hr; use equianalgesic chart
TDD new (desired opioid) = TDD current opioid * (EF of new opioid/EF of current opioid) EF = equianalgesic factor
Step 4: reduce 24 hour dose by 1/3rd (range is 25-50%) if ≤5/10 pain scale when switching to account for interpatient variability and incomplete cross tolerance
Step 5: select appropriate dosing interval
Step 6: select appropriate BTP dose by multiply by 10% of their overall (24hr) opioid amount
- use 10-20% of 24h dose; offer no more frequent than time it takes to reach Cmax po/pr q1h SC/IM q30min IV q10-15min

Fentanyl conversion X mg OME/d * 0.5 = X mcg/hr TD
25mg OME/d ≈ 12.5 mcg/hr TD 50mg OME/d ≈ 25 mcg/hr TD 100mg OME/d ≈ 50 mcg/hr TD 150mg OME/d ≈ 75 mcg/hr TD 200mg OME/d ≈ 100 mcg/hr TD

*PS 48yo with chronic back pain due to MVA. Well controlled (2/10) on Oxycontin 20mg bid and oxycodone 5mg q44h prn (avg 3/day). Switch to morphine ER/IR.
1. current: oxycodone ER 20mg bid and BTB oxycodone 5mg q4h prn (average 3/day)
2. current: oxycodone ER = 40mg + oxycodone IR 5mg*3 (15mg) = 55mg total 24 hour oxycodone
3. TDD new (morphine) = oxycodone 55mg * ($EF_{morphine}$ 30mg/$EF_{oxycodone}$ 20mg) = 82.5mg total 24 hour morphine
4. 82.5mg * 0.67 = 55mg morphine (since pain score ≤5/10, lower by 1/3rd)
5. 55mg morphine in 24 hours → 30mg morphine ER bid
6. 60mg * 0.10 = 6mg morphine → 5mg morphine IR q3h prn

Neuropathic Pain

Definition of Neuropathic Pain

A type of pain that is caused by damage to or dysfunction of the nervous system
  – Cannot be explained by a single disease process or a single specific location of damage – Exact mechanism is unknown

Pathophysiology of Neuropathic pain

- Peripheral origin (e.g Chemotherapy)
  - Abnormal nociceptor sensitization and ectopic impulse generation
  - Decreased threshold due to nerve injury
  - Increased sensitivity to afferent neurons to sympathetic system activation

- Central origin (e.g Spinal cord injury)
  - Central sensitization of nociceptors in spinal cord

Common causes of neuropathic pain

- Diabetic neuropathy
- Cancer related neuropathy
  - Breast cancer, lung cancer, multiple myeloma, brachial plexus neuropathy
- Chemotherapy induced neuropathy
  - Cisplatin, paclitaxel, vincristine, vinblastine, oxaliplatin
- Post radiation neuropathy
- Post herpetic neuropathy
- Other causes: nutritional deficiencies, HIV, SC injury, alcohol-induced, surgery neuropathy (post mastectomy syndrome, post thoracotomy syndrome)

Assessment of neuropathic pain

- Quality: Burning, tingling, stabbing, lancinating, shooting
- Other assessment features: Decreased reflexes, allodynia, weakness, muscle atrophy

Management of Neuropathic Pain

- Management of neuropathic pain is complicated
  – Complicated dosing
  – Delayed onset of action
  – Many treatment side effects
  – Coexists with other types of pain
  – Medication efficacy is unpredictable
- Treatment of neuropathic pain
  – Adjuvant analgesics
  – Traditional opioid agents are second or third line

Adjuvant Analgesics

- Definition: Agents with characteristics that provide benefit in pain management, though they are not classified as analgesics
- Medications that supplement primary analgesics
  –May themselves be primary analgesics
  –Use at any step of WHO ladder
- Medications for neuropathic pain should be patient specific
- In addition to efficacy, consider following factors when selecting therapy:
  – Comorbid conditions that may benefit from therapy
  – Medication tolerability (side effects)
  – Potential medication interactions
  – Risk for medication abuse
  – Risk for overdose
  – Cost of therapy

First-Line Agents

- Secondary Amines
  - Nortriptyline (Pamelor®)
  - Desipramine (Norpramin®)
- Calcium Channel Ligands – best for stabbing neuropathic pain
  - Pregabalin (Lyrica®)
  - Gabapentin (Neurontin®)
- SNRI
  - Duloxetine (Cymbalta®)
  - Venlafaxine (Effexor®, Effexor XR®)**

Tricyclic Antidepressants (TCAs): Secondary Amines: Desipramine (Norpramin®), Nortriptyline (Pamelor®)
- May also benefit patients with: Depression and insomnia
- Side effects: Anticholinergic effects, Increased risk of sudden death
- Caution: Use in patients with cardiac disease, suicide risk, and seizure risk

Calcium Channel Ligands: Pregabalin (Lyrica®), Gabapentin (Neurontin®)
- May also benefit patients with: Insomnia
- Side Effect: Fairly well tolerated; Somnolence, dizziness, peripheral edema
- Caution: Use in renal insufficiency (dose adjustments)

Second/Third-Line

Optional anticonvulsants for neuropathic pain: Tiagabime (Gabitril®), Topiramate (Topamax®), Lamotrigine (Lamictal ®), Levetiracetam (Keppra®), Zonisamide (Zonegran®), Oxcarbazepine (Trileptal®), Divalproex Na (Depakote®), Carbamazapine (Tegretol®)

- Duloxetine (Cymbalta®)
  - Caution use in hepatic and renal dysfunction
  - Also approved for chronic musculoskeletal pain due to low back pain and OA
- Venlafaxine (Effexor®, Effexor XR®)
  - Caution use in cardiac disease
  - May also benefit patients with: Depression
- Side Effects fairly well tolerated: Nausea, Insomnia, Constipation/diarrhea

desipramine nortriptyline	start 25mg qhs (10mg geriatric or sensitive) max 100-150mg/d	inhibits NE and 5HT reuptake; blocks Na Ca channels and NMDA receptors	ACh effects, sedation, OH	caution CVD analgesic dose less than ADT dose titrate slowly
gabapentin	2400-4800mg/d	bind to α2-δ subunit of voltage-gated Ca channels to reduce Ca-dependent release of neurotransmitters good for stabbing neuropathic pain	somnolence, dizzy, depression, peripheral edema, tremor	minimal DDIs; can be $$ renal dose adjustment relative 'good' SE profile titrate slowly
pregabalin	50mg tid or 75mg bid (max 300-600mg/d)		somnolence, dizzy, peripheral edema	
duloxetine	60mg qday	selective NE 5HT reuptake inhibitor	nausea, insomnia, constipation/diarrhea	caution renal and hepatic avoid abrupt discontinuation benefits in comorbid depression

Lidoderm Patch (5%)
- Use in pain relief associated with postherpetic neuralgia – First line option for localized peripheral neuropathic pain
- Directions for use:
  - Apply patch to most painful area
  - Up to 3 patches may be applied in a single application
  - Patch(es) may remain in place for up to 12 hours in any 24-hour period
  - Remove patch while having MRI scan; can cause burns

- Blocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction

Opioids:
- Use in short-term neuropathic pain: hydrocodone or oxycodone
- Methadone:
  - Inhibits the re-uptake of serotonin and norepinephrine
  - Active N-methyl-D-aspartate (NMDA) receptor antagonist
  - Utilized for resistant neuropathic pain or in patients with difficult to manage mixed pain

- Antiarrhythmic: Mexiletine (Mexitil®), orally administered lidocaine analogue
- TCAs: Tertiary Amines: Amitriptyline (Elavil®), Doxepin (Sinequan®)
- GABA Agonists: Baclofen (Lioresal®)
- Alpha-2 Agonists: Clonidine (Catapres®)

Butorphanol (I.M.) – 2 mg
Codeine (oral) – 200 mg
Codeine (I.M.) – 100 mg
Fentanyl (I.M.) - 100 **mcg**
Hydromorphone (oral) - 7.5 mg
Hydromorphone (I.M.) - 1.5 mg
Levorphanol (oral) - 2 mg
Meperidine (I.M.) – 100 mg
Morphine (oral) - 30 mg
Morphine (I.M.) - 10 mg
Nalbuphine (I.M.) – 10 mg
Oxycodone (oral) - 20 mg
Oxymorphone (oral) - 10 mg
Oxymorphone (I.M.) - 1 mg
Tapentadol (oral) – 100 mg

https://en.wikipedia.org/wiki/Nociceptor#Location

Headache

Pathophys
Headache is a pain that results from disturbance of **pain sensitive structures** in the head; brain tissue is not pain sensitive; some intra/extracranial sources
- intracranial structures:
- extracranial structures

Diagnoisis
"if you have 30 minutes to see a patient with headache, spend 29 on **history** and one on the exam"
- type/number, when/how, frequency (episodic vs. paroxysmal), location/spread, severity, quality (sharp, throbbing), associated sx (NV photophobia), triggering factors, previous evaluation, previous treatment/medications, measures to reduce pain, PMH FH SH
- vital signs (BP, low oxygen), systemic diseases; neuro exam (visiual field defect, papilledema, focal findings-speech/sensory/hemiparesis) = mass/pressure
- serological testing; neuroimaging (CT look for cerebral bleed, MRI tumors cysts masses inflammation)

IHS Classification of Headache (ICHD-3)
I. Primary headaches (unknown cause): migraine, tension-type headache (TTH), trigeminal autonomic cephalgias (TAC), other primary headaches
II. Secondary headaches (known cause, treat/cure cause): attributed to substance/withdrawal
III. Painful cranial neuropathies, other facial pain and other headaches

Headache Algorithm*
headache
- paroxysmal - "benign"
- daily
  - new onset - "immediate attention"
  - chronic - "usually benign"

Migraine headache
- a paroxysmal pain on one side of head, often associated with nausea and followed by pain-free intervals
  - usually has comorbid diseases: neuro, psych, cardio, GI, asthma, allergies
  - half patients with diagnosis are not medications (using OTCs)

Migraine Diagnostic Criteria: Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia
- quality: **throbbing**; **unilateral**; associated with **NV**, **photophobia**, **phonophobia**; aggravation by physical activities
- paroxysmal headache but attacks get milder and less frequent in later years
- age of onset: any age; attack mostly commonly teenage; 90% first attack by 40yo; can start in older patients (R/O other causes); FH in 90%

Migraine Triggers
- altered sleep pattern, stress, menses, alcohol, irregular life schedule, caffeine, chocolage, foods containing MSG tyramine nitrates

Classification
1. migraine without aura (aka common migraine)
2. migraine with aura (aka classical migraine)
   a. migraine with typical aura:
      - typical aura with headache
      - typical aura without headache
   b. migraine with brainstem aura
   c. hemiplegic migraine: weakness one side of body (stroke?)
      - familial hemiplegic migraine (FHM) 1,2,3
      - sporadic hemiplegic migraine
   d. retinal migraine
3. chronic migraine: how freq headache going on (>15d/mo, irregardless of how long its been going on)
4. complications of migraine
   a. status migrainosus
   b. persistent aura without migraine
   c. migrainous infarcation
   d. migraine aura-triggered seizure
5. probable migraine
6. episodic syndromes that maybe associated with migraine
   a. recurrent GI disturbance
   b. benign paroxysmal vertigo
   c. benign paroxysmal torticollis (muscle contract)

Tension-Type Headache (TTH)
- aka muscle contraction headache; most common type
- pathophys: emotional tension and muscle contraction; central mechanism
- diagnosed based on what it is not
- quality: bilateral headache, chronic or episodic, tight band around head, waxes and wanes is severity, no *aggravation by physical activity*, no nausea
- classification: - infrequent episodic TTH - frequent episodic TTH - chronic TTH - probable TTH

Cluster Headache
- most painful recurrent headache; uncommon (migraine 10-50x more freq); M>F 5:1; age of onset 1-70yo 3rd decade; alcohol/tobacco triggers
- pathophys: vascular headache
- clinical features: onset at night, lasts 1-2hr, many attacks during 24hr period;
  - severe "suicide headache", unliateral behind eye, restless, tearing from ipsilateral eye in addition to redness, ptosis (drooping eye) and miosis
- classification:
  - episodic cluster headache: daily attacks for days, weeks, months followed by attack free period
  - chronic cluster headache: attacks for more than a year without remission for >2 weeks

Medication Overuse Headache (MOH)
- aka analgesic rebound HA, medication-induced HA, analgesic-induced HA, "Tylenol" HA
- caused by excessive use of analgesics: >3x/week - 0.7-1.7% of all HA, 20% of chronic HA
- symptoms similar to TTH (fluctuates throughout day); majority transformed from episodic migraine

- overlooked frequently by HCP; usually mixed with another headache

Headache associated with a Mass
- daily headache, location based on area of mass lesion; required immediate medical attention
- can be associated with morning NV if increased intracranial pressure (d/t gravity); can be associated with focal neurological sx based on location of mass

Headache requires urgent evaluation
- alteration of consiousnesss: hemorrhage (subarachnoid, subdural, epidural, parenchymal); infection (meningitis, encephalitis)
- giant cell arteritis (temporal arteritis) can lead to blindness, act quick admin steroids to prevent blindness

Chronic Daily Headache (CDH)
- spectrum of headaches, 4% prevalence; lasting >3mo - causes: chornic TTH, chronic migraine, MOH
- chronic = more days than not in a month for paroxysmal HA

Role of RPh
- determine immediate need (new onset HA, HA associated with LOC or focal neurological sx)
- educate about headache triggers; help avoid excessive use of analgesics

Treatment
Goals: relieve the pain; restore function of patient
Types of treatment
- etiology based "treating the cause of the HA": for secondary HA like surgery (tumor, bleed), antibiotics, medication-induced, treatment of inflammation
- symptomatic "treating the pain but not cause": acute treatment prn, prophylactic treatment
Unique HA treatment: cluster, indomethacin-responsive HA, MOH, trigeminal neuralgia (triggered by eating, touching face, electric shock pain), TTH, migraine

Cluster headache
- acute: 100% oxygen, steroids, dihydroergotamine (DHE), triptans, intranasal lidocaine
- prophylactic: lithium carbonate, CCBs, galcanezumab

Indomethacin-responsive headache
- striking/excellent response to indomethacin 25-250mg
- headaches include: primary stabbing HA, hemicrania continua, paroxysmal hemicrania, primary exercise HA, primary cough HA, primary HA sexual activity

Medication overuse headache
- stopping all "as needed" analgesics: gradual, abrupt
- reassurance and education; establish expectation; may use NSAID as briding; may use TCA; treat underlying headache

Trigeminal Neuralgia
- carbamazepine or oxcarbazpine
- microvascular decompression (MVD)

Tension-type headache
- scalp and neck relaxation techniques; reassurance and education
- for occasional mild HA: aspirin, acetaminophen NSAIDs
- prophylaxis: amitriptyline 50-150mg DOC; other options for prophylaxis

Migraine
- individualize plan, set expectation, actively engage patients, prevent MOH
- nonpharm: education about triggers, sleep, regulating life schedule; make migraine calendar
- pharm overview: - treatment during acute attacks (abortive treatment) which is treating pain or associated sx like NV - prophylactic (preventive) treatment

Treatment of acute attacks
- aka abortive treatment; most critical step; goals: relieve pain and restore function; keys to successs: initiate treatment rapidly
  - treatment of pain: step vs. stratified care
  - treatment of NV: antiemetic agents; preferably rectal

1. simple analgesics, combo with caffeine
2. narcotics
3. ergot derivatives: DHE nasal spray, ergotamine/caffeine
4. triptans (serotonin 5HT 1B/1D receptor agonists); treats migraines exclusively; safe/well-tolerated; contraindicated in CAD, CVD, uncontrolled HTN
   - moa: cranial vasoconstriction, peripheral neuronal inhibition; inhibition of transmission of the trigemiocervical complex
   - "migraine killers"; triptans restore function, no risk for dependence/abuse, work rapidly, safe; >89% of migraines are severe (no response to OTCs)
   - ppl say concern with serotonin syndrome but since using intermittently not a worry
   - most of time gradual build up of headache over 40min, so use oral once feeling symptoms early
   - though sometimes, can be rapid therefore use nasal spray or SC
   - ask how soon the peak hits, guides which route of administration - sumatriptan 25-50-100mg PO 6mg SC 20mgNS - zolmitriptan 2.5-5mg PO 5mg NS
5. gepants (CGRP receptor antagonists): ubrogepant, remigepant
6. ditans (serotonin 5HT 1F receptor agonists): lasmiditan; can be used in patients with CAD/CVD/HTN

Triptan failure
- proper use/admin; give it one more chance; try more than one triptan (use 3 before failure); add NSAIDs
- use gepants, DHE, other abortive treatments; help pt stay out of ERs (rescue medications)

Prophylactic treatment
- decreases frequency, makes migraines shorter and less severe; make it more responsive to abortive treatment
- indicated when migraine frequency is high (?), maybe 2-3 migraines/mo
- can be considered even if frequency is not high: migraine aura, migraine without HA, very debilitating migraines
- prophylaxis decreases frequency: improves QoL, improves productivity - prevent migraine progression? not really - prevent MOH

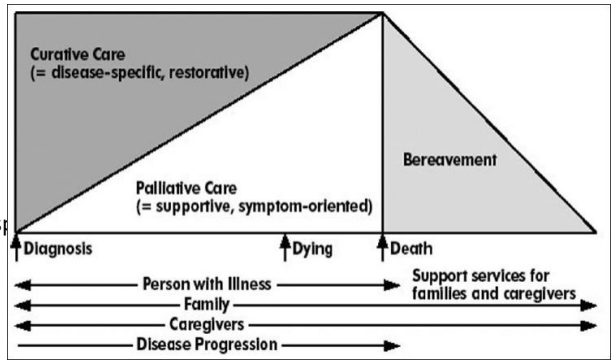
- valproic acid - topiramate - propranolol - timolol - onabotulinum toxin A - CGRP inhibitors (erenumab, eptinezumab, fremanezumab, galcanezumab)
others: amitriptyline, gabapentin, CCBs, SSRI, Mg, vitamin B2, butterbur, feverfew

Selecting: non head to head comparison; decision based on cost, compliance, SE, comorbidities

https://www.uptodate.com/contents/pathophysiology-clinical-manifestations-and-diagnosis-of-migraine-in-adults
https://www.uptodate.com/contents/evaluation-of-headache-in-adults
https://www.uptodate.com/contents/acute-treatment-of-migraine-in-adults

Palliative and Hospice Care

- Define palliative and hospice care
- Differentiate medication selection principles for non-hospice and palliative/hospice patients
- Recognize a typical clinical scenario/picture for a hospice patient
- State the most common hospice diagnoses and their symptoms
- Review the role of a pharmacist on a palliative care/hospice interdisciplinary team
- Identify and utilize important factors in determining appropriate use of medications in palliative/hosp
- Evaluate patient specific therapy and provide recommendations



List 5 Palliative Care Diagnosis

Service Provided Example

Role of Pharmacist

1. Drug information: Answer both patient specific and more general disease and medication based questions
2. Educational programs: Give educational seminars/audio conferences to healthcare professionals that provides education (often times continuing education credit) on a topic
3. Assistance in symptom management & medication therapy management: Provide recommendations for patients with symptoms common at the end of life (pain, NV, agitation)
4. Determination of medication coverage: Guide the hospices as which medications are required by Medicare to cover according to the hospice diagnosis
5. Cost considerations: Develop guidelines for hospices to implement for the use of high cost medications such as the IV bisphosphonates and intra-spinal pain pumps

Detailed Medication Review

• Dosage Errors • Drug interactions • Duplication of therapy • Significant side effects • Ineffective drug therapy
• Determination of medication coverage • Assistance with symptom management • Comments

DM FPG 150-200

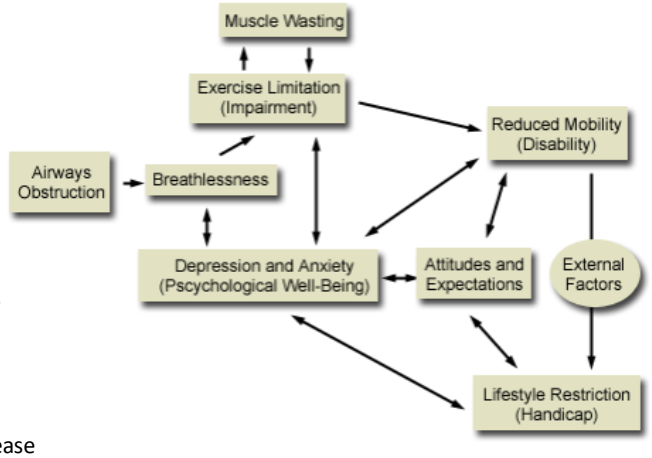
Dyspnea

• Defined as an uncomfortable awareness of breathing by the patient
• Three important aspects 1. Subjective 2. Multidimensional (Physiological, Psychological, Environmental factors) 3. Multiple distinct sensations
• Prevalence in life-threateningly illness: 12 – 74%; More likely as death approaches

• Subjective– Poorly correlated to respiratory rate, pO2, and blood gas concentrations
• The only reliable measure is patient self-report
• Multiple Distinct Sensations– Described as air hunger, feeling of suffocation, chest tightness, increased effort, rapid breathing

• Has a large impact on quality of life: – Limit social activities – Decreases functional status – May diminish the will to live
• Treatment goals: – Improve the patient's symptoms while minimizing side effects from medications

• Assessment of possible patient factors cannot be over emphasized
• Assess for potential causes and treat if possible – Anemia – Anxiety – Infections – Secretions – Fluid overload – Bronchospasm – COPD exacerbation



Biopsychosocial model of dyspnea management
Symptom assessment → Is disease modifiable?
Yes: alleviate symptom through disease-specific intervention (consider global) → review
No: alleviate symptom through global/systemic intervention → review

• Non-Pharmacologic Interventions
• Open window • Respiratory muscle training • Adjust the room temperature
• Eliminate environmental irritants • Keep line of sight clear to outside
• Limit the number of people in the room • Behavioral approaches, eg, relaxation techniques
• Oxygen?

Management of Breathlessness: Symptomatic management
• Opioids: First line therapy when no treatable cause can be identified; Low dose immediate release
MoA: reduce response to the dominant respiratory control center within CNS, which is CO_2 sensitive;
→ decreased normal response to afferent stimuli that increase respiratory rate
the driver for us to breathe is increasing CO_2 concentrations, so CO_2 rises you get stimulated to breathe so you breathe harder, more efficient
- so low doses, blunt response so it takes little more CO_2 buildup before they begin to feel short of breath
- decrease medullary sensitivity to hypercarbia or hypoxia
- blunted medullary response to hypercarbia or hypoxia
- Additional proposed mechanisms of action of opioids:
• Histamine release and depression of sympathetic vasculature reflexes causing arteriolar and venodilation
Result: reduction in cardiac pre- and after-load
• Central opioid action of relaxation
Result: Decrease in anxiety
• Relief not related to respiratory rate
• No ethical or professional barriers
• Low dose immediate release products
• Morphine 2.5-20 mg po/SL q 1h prn
• Oxycodone 2.5-20 mg po/SL q 1h prn
• Role for extended release?? Nebulized opioids?? nah
• Break Anxiety-Dyspnea Cycle: Low dose Anxiolytics ATC + PRN

Dyspnea: Bilateral Wheezing
• Bronchodilators: albuterol, ipratropium (Atrovent)
• Corticosteroids:
• Oral better than inhaled in end-stage disease; may not have adequate lung function to inhale corticosteroids; risk of oral thrush with ICS
• Dexamethasone
• Prednisone
• Anxiolytics
• Low doses are safe in combination with opioids
• Best to start with prn or a test dose: Lorazepam (Ativan®) 0.25-2 mg po q 6-12 h ATC
• For acute exacerbation: q1h prn until settled; best to start q 8-12 hours. Rarely need to shorten dosing interval--can increase dose instead.

Nebulized Furosemide
• Furosemide injection – 20mg mixed with 1mL Normal Saline – Nebulized QID
• Hypothesized mechanism of action
– Enhance pulmonary stretch receptor activity inhibition of chloride movement through the membrane of the epithelial cell
– Increased synthesis of bronchodilating prostaglandins

Top Hospice Diagnosis: 1.Cancer – 30% 2.Heart – 17.4% 3.Dementia – 15.6% 4.Other – 14.7% 5.Respiratory – 11% 6.Stroke – 9%

Unique Hospice Considerations • Eating at the end of life • Oxygen for symptom control

Substance use Pcol

Substance use disorders have cognitive behavioral, physiological symptoms; continue using despite significant problems; underlying change in brain circuits that may persist beyond detox; relapses and intense drug craving when exposed to drug-related stimuli
Addictive drugs are rewarding and reinforcing
- reward stimulus: interpreted intrinsically positive or something to be approached
- reinforcing stimulus: increases possibility that behaviors paired with it will be repeated; not all reinforcers are rewarding; negative stimulus can reinforce avoidance behaviors
    - self-admin paradigm: press bar to get drug; strength of reinforcement indicated by amount of work does to get drug

Generally, short-acting drugs more addicting than long; more rapid rise in drug concentration at synapse greater addiction potential; more intense intoxication and escalating pattern

Drug-induced pleasurable states are important motivators of drug use: Produce feelings of pleasure ("high")
Direct activation of the brain reward system; Can be so intense that normal activities may be neglected
Instead of achieving reward system activation through adaptive behaviors, drugs of abuse directly activate the reward pathways
Long-term use can produce undesirable changes in brain reward circuitry

The best-established pathway for reinforcement: 'Reward Pathway'
The dopaminergic projection from the **ventral tegmental area (VTA) to the nucleus accumbens** (sever this connection, less addicting)
Dopamine neurons originate (cell bodies) in the VTA and send axons to nucleus accumbens (where dopamine is released)
Most (maybe all?) drugs of abuse cause elevation of dopamine levels in the nucleus accumbens; Even though act at many different types of neurotransmitter systems and receptors

Craving
Intense desire or urge for the drug ; Associated with activation of reward pathway ; Exact mechanisms are unknown ; Persistent and very difficult to treat
More likely when in an environment where the drug previously was obtained or used
Classical conditioning
A particular location or environment or cues (like syringe or cigarette) associated with the pleasurable experience of drug taking
The associated stimulus itself evokes the response (like Pavlov's dogs)

Pg 406-407

Concept of Disinhibition: May explain how inhibitory drugs can increase dopamine release in nucleus accumbens
Inhibition of an inhibitory neuron (usually a GABA releasing neuron) can ultimately lead to increased activity of the downstream neuron (and increased DA release)
Pg 409 Neuropharmacologic classification of addictive drugs by primary target

Drugs with potential for misuse or addiction
--nicotine, sedative/hypnotics/anxiolytics, stimulants, opioids, ketamine phencyclidine (PCP), inhalants, caffeine, alcohol, GHB, cannabinoids, hallcuinogens, MDMA

Caffeine
increased mental alertness/reduced fatigue, improved athletic mental performance
short term adverse effects: headache, anxiety, tremors, insominia
withdrawal: headache common
MoA: antagonist at adenosine A1 and A2 receptors
  adenosine receptors are G protein linked (metabotropic)
    adenosine A1 receptors: inhibition of adenylate cylase
    adenosine A2 receptors: activation of adenylate cyclase
adenosine decreases during slow wave sleep and increases after prolonged wakefulness
  during sleep deprivation, adenosine accumulates in basal forebrain and promotes sleep by inhibiting cholinergic neurons
  adenosine may mark the duration of wakefulness and signal increased need for sleep
Caffeine antagonizes the inhibitory action of adenosine and would promote alertness

Alcohol
At low to moderate concentrations: Anxiolytic effects, feeling of well-being, euphoria
  Initial effects of alcohol are believed to result from
    - Facilitation of GABA-A receptors
    - Inhibition of NMDA glutamate receptors

At higher concentrations: Slurred speech, ataxia, impaired judgment, disinhibited behavior ('drunkenness')
  At higher doses, ethanol can inhibit the functioning of most ligand-gated and voltage-gated ion channels
    - May be due to generalized effect on cell membranes
    - Since channels are in membranes, disruption of lipids could affect various channel properties

TABLE 83-2 Specific Effects of Alcohol Related to Blood Alcohol Concentration

BAC (%)	Type of Impairment	Effect(s)
0.0–0.05	Mild	Mild speech/memory/attention/coordination/balance impairment, relaxation, sleepiness
0.06–0.15	Increased	Impaired speech/memory/attention/coordination/balance, risk of aggression, significantly impaired driving skills, increased risk of injury to self and others, moderate memory impairment
0.16–0.30	Severe	Impaired speech/memory/attention/coordination/reaction time, balance significantly impaired, driving skills dangerously impaired, judgment and decision making dangerously impaired, blackouts, vomiting and signs of alcohol poisoning common, loss of consciousness
0.31–0.45	Life-threatening	Loss of consciousness, danger of life-threatening alcohol poisoning, significant risk of death

Treatment of alcohol withdrawal detoxification
Benzodiazepines are used
Rationale: Ethanol and benzodiazepines have similar effects on CNS function (GABA-A receptor)
Reduce chance of seizures during withdrawal; Also helps treat insomnia, anxiety, delirium

Liver metabolism of ethanol
Alcohol dehydrogenase: Ethanol → acetaldehyde
Aldehyde dehydrogenase: Acetaldehyde → acetic acid

'Aversion' therapy: Disulfiram (Antabuse) is an aldehyde dehydrogenase inhibitor
Accumulation of acetaldehyde produces toxic effects and aversion to alcohol; Tachycardia, hyperventilation, panic, distress, flushed skin (unpleasant but not harmful)

Drugs to reduce alcohol craving (difficult to treat)
Naltrexone (ReVia): Competitive antagonist at opioid receptor sites; Thought to block alcohol-induced activation of dopaminergic reward pathways
  - Role of endogenous opioids in alcohol addiction?
Acamprosate (Campral): Appears to increase the activity of the GABA-ergic system, and decrease activity at N-methyl D-aspartate (NMDA) glutamate receptors

Gamma hydroxybutyrate (GHB)

CNS depressant – overall cause inhibitory effects on neuronal function
GHB can serve as both a precursor and a degradation product of GABA

The sedative and amnestic onset of effect is rapid; Particularly when combined with alcohol or other depressants
Dangerous for the voluntary and involuntary (assault victim) user ; Can also cause respiratory depression

GHB is a weak GABA-B receptor agonist and is also an agonist at "GHB receptor"
- Both receptors are metabotropic (inhibitory G protein)
- Facilitate opening of potassium channels/closing of calcium channels
  - Would decrease neuronal activation and/or transmitter release
- GHB receptor is relatively uncharacterized

Sodium Oxybate (Xyrem): An approved use of gamma hydroxybutyrate (GHB)
Indications: cataplexy and excessive daytime sleepiness (EDS) in narcolepsy
Cataplexy = sudden and temporary muscle weakness and loss of tone (often in response to strong emotions)
FYI: Cataplexy patients instructed to lie down and sleep after each dose of sodium oxybate; Taken immediately before bedtime and again 2.5 to 4 hours later
"Do not drive a car, use heavy machinery, fly an airplane, or do anything that is dangerous or that requires you to be fully awake for at least 6 hours after you take Xyrem"
Xyrem is available only by prescription and filled through the central pharmacy in the 'Xyrem Success Program'

Cannabis/Marijuana/THC

Derived from Cannabis sativa plant (hemp); Delta-9-tetrahydrocannabinol (THC); One of several cannabinoid compounds in marijuana
THC is primarily responsible for psychoactive effects of marijuana: Euphoria, Sometimes depressive behavior, Introspection and sense of time moving slowly, Distortion of sensory perceptions, Hallucinations possible, Possible impairment of short and long term memory, Impaired motor coordination possible

Cannabinoid signaling
CB1 receptor: metabotropicgenerally inhibitory coupled through Gi protein to…
- Inhibition of adenylate cyclase - Inhibition of calcium channel activation - Facilitation of potassium (K+) channel activation
Unusual transmitter mechanism: anandamide is synthesized when needed (not stored and released from vesicles)
Postsynaptic calcium influx activates phospholipase D (PLD), which then acts on N-arachydonoylphosphatidylethanolamine (NAPE) to produce anandamide
Anandamide: An endogenous neurotransmitter ligand for CB1 receptor
- Anandamide is mainly a retrograde transmitter
- Anandamide is synthesized postsynaptically and acts presynaptically (CB1 receptor)
- Anandamide activates presynaptic CB1 receptors to inhibit neurotransmitter release
- Anandamide is metabolized by fatty acid amide hydrolase (FAAH) to arachidonic acid and ethanolamine
  - drugs in future may block FAAH, which would increase anadamide levels, boost cannabinoid signaling of drugs like THC

Anandamide has analgesic action in animal models of pain; Historically, marijuana has been used as an analgesic
Use of marijuana for appetite stimulation (in HIV patients), for glaucoma, and to treat nausea in chemotherapy
Dronabinol (Marinol) = delta-9-THC
(FYI) Rimonabant (Acomplia): CB1 receptor antagonist developed as appetite suppressant; Withdrawn from EU due to reports of severe depression/suicidal thoughts. Not approved US

Hallucinogens

Lysergic acid diethylamide (LSD) = synthetic chemical Mescaline = derived from peyote cactus Psilocybin = derived from a mushroom
Partial agonists at 5-HT2A serotonin receptors
- Primarily visual hallucinations/can be auditory too
- Sensory and perceptual distortions: Perceived visual representation of sounds and tactile stimuli, Time dilation-subjective sense of slowed time, Ego dissolution-altered sense of self, Mystical sensation of being united with some larger spiritual phenomenon

LSD intoxication was compared to schizophrenia
LSD is not a great model for psychosis, though:
- Intoxication is transient - Can elicit euphoria/other positive emotions - Schizophrenia-hallucinations are mostly auditory - LSD does not cause fixed or elaborate delusions
Have been studied as an adjunct to psychotherapy: new interest developing lately

MDMA

3,4 methylenedioxymethamphetamine
Combination of psychostimulant-like and weak LSD-like effects
- Increased energy - Increased tactile sensitivity - Empathic feelings - Altered sense of time/mild hallucinations
Psychedelic (LSD-like effects) likely due to effects on serotonin transporter
Negative effects: Tachycardia, hypertension, jaw clenching, agitation, hyperthermia; Serotonin syndrome possible
Reported to produce lesions of serotonin neurons in animals; Neurotoxic effects possible in humans

Substance Use Disorders

1. Discuss relevant terminology, epidemiology, and pathophysiology of opioid use disorder (OUD) and alcohol use disorder (AUD)
2. Recognize harm reduction strategies related to substance use disorders (SUD)
3. Compare qualitative and quantitative urine drug screens and recognize their place in therapy
4. Summarize pharmacological treatment options for OUD and AUD
5. Apply knowledge and skills to case-based scenarios related to OUD and AUD

Tolerance: occurs when a person using a drug begins to experience a reduced response to the medication, requiring more of that drug to experience same effect
Dependence: occurs when the body adjusts its normal functioning around regular use of drug, resulting in unpleasant physical symptoms when the drug is stopped

OUD AUD DSM-5: presence of at least 2 symptoms in last 12 months; mild 2-3sx moderate 4-5sx severe 6+sx

Risk factors for SUD: genetics, environment (early trauma, stress, adverse child experiences, easy access), untreated psych disorders, past misuse

Pathophys
- OUD/AUD chronic relapsing disease of brain; relapse is common; relapse serves as sign for resumed, modified, new treatment

DA going to VTA then to nucleus accumbens then prefrontal cortex; DA responsible for reinforcing effects; long-term use get DA receptor down-regulation
  - prefrontal cortex area of brain responsible for judgement/decision making: disruption = reduced impulse control and continued use despite consequences

GABA inhibitory in brain (activation = sedation/relaxation); alcohol mimics GABA and inhibits glutamate activity; overstim can lead to extreme sedation/toxic
  - prolonged exposure to alcohol desensitizes GABA receptors and makes NMDA hypersensitive to glutamate

Urine Drug Screens
immunoassay: screening only (qualitative yes/no, prone to false tests)
GC/MS: confirmation test (quantitative, very sensitive, minimal falses)

codeine 2d heroin (detected as morphine) 2d methadone 3d marijuana single use 2-7d, chronic 1-2mo cocaine 2-4d methamphetamine 1-2d
benzos SA 3d, LA/chronic 4-6wk alcohol 1-12hr hydromorphone 2-4d hydrocodone 2-4d oxycodone 2-4d fentanyl 2-3d tramadol 1-4d

Expected Metabolites
heroin → 6-monoacetylmorphine (6-MAM) short HL → morphine → hydromorphone
codeine → morphine, hydrocodone
morphine → hydromorphone
hydrocodone → hydromorphone
oxycodone → oxycodone, noroxycodone
fentanyl → norfentanyl
buprenorphine → norbuprenorphine
tramadol → O-desmethyltramadol (M1)

Treatment of OUD AUD

Medication-Assisted Treatment (MAT): combination of medication and behavioural therapies to treat OUD

FDA-approved to treat OUD: methadone, naltrexone, buprenorphine
- methadone full mu agonist (bind to and activate receptor resulting in maximal effect with increasing doses)
- naltrexone: mu antagonist (bind to receptor, but do not activate it)
- buprenorphine: partial mu agonist (bind to and activate receptor, but to lesser extent than full agonists; ceiling effect)

<u>methadone</u>
- most widely used/studied
- associated with higher rates of treatment retention and lower rates of illicit opioid use than none or placebo
- opioid treatment programs (OTP):
  - 18yo+ meet DSM-5 OUD 1yr hx, voluntary, written informed consent;
  - <18yo two documented, supervised, unsuccessful withdrawals or treatment without OUD medication; parent consent

dosage: liquid most common in OTP, can use tablets outside for pain relief
MoA: full mu agonist; reduces opioid craving and withdrawal, blunts/blocks effects of illicit opioids, increased doses causes maximal effect (no ceiling)
Dosing: goal: lowest dose possible that effectively eliminates withdrawal symptoms, but does not cause sedation or intoxication; individualized, low and slow
SE: dizzy, sedation, constipation, N, sweating, itching, sex dysf
CI: respiratory depression, acute/severe asthma, GI obstruction
Precautions: may cause resp dep (monitor during initation/increased dose; concurrent benzos, alcohol)
- can prolong QTc/cause cardiac arrhythmia; can cause sedation, potential for misuse; physical dependence; has many DDIs

DDI: CNS depressants, 3A4 inhibitors/inducers, QTc prolongers, antidepressants, anticholinergics, partial opioid agonists

<u>naltrexone</u>
Dosage: ER naltrexone (Vivitrol) IM q4wk for both OUD AUD; oral naltrexone (ReVia) not widely used for OUD; may take oral while waiting
- Vivitrol more effective than none or placebo in reducing risk of return; patients must be opioid-free for period of time; cannot be diverted
- 380mg once monthly into gluteal (4ml); must be clean for 7-10d (short-acting opioids), 10-14d (long-acting opioids) before intiating naltrexone

MoA: does not activate mu receptor, blocks it; does not alleviate withdrawal symptoms; blocks other opioids being used
- can precipitate withdrawal after recent opioid use;
- naloxone/naltrexone challenge: either administered to assess if patient physically dependent to opioids prior to administration of ER naltrexone

SE: injection site rxns, body aches/pains, insomnia, HA, N, liver enzyme abnormal, sore throat, nasal congestion
CI: current opioid use; acute opioid withdrawal, severe hepatic impairment; failed naloxone/naltrexone challenge; urine drug positive
Precaution: injection site rxns (pain, redness, swell, bruising); precipitate withdrawal in recently used opioids
- patients are at risk for opioid overdose at end of 4-week dosing period
- patients who override naltrexone blockade at risk of overdose
- monitor liver function, caution renal impairment; monitor worsening depression/suicide
- patient should carry medical card indicating they are being treated with naltrexone

REMS program aware of risks: risk of opioid overdose, injection site rxn, precipitated withdrawal, hepatotoxicity

<u>buprenorphine +/- naloxone</u>
- naloxone added to decrease potential for misuse; but questionable utility given that buprenorphine has higher affinity for mu than naloxone

Dosage: SL tabs, SL films, buccal films, patch, implant, SC (Sublocade)
- transmucousal (films, SL) initiated when patient is showing clear signs of withdrawal; target maintenance 16-4mg/day; okay office or home initiation
  - home: waits until signs of moderate withdrawal signs
  - office: induction day 1: initial 2-0.5mg or 4-1mg, titrate 2-4mg increments q2hr based on withdrawal; titrate to 8-2mg; day 2 up to 16-4mg single or dd
- depot (implant, SC) inducted first on transmucousal product prior to; consider good for diversion or safe storage concerns or hard to see provider
  - Sublocade: induction 8-24mg transmucosal for minimum 7days; initial 300mg qmo x2mo, maintenance 100mg qmo, can increase to 300mg
    - REMS: never dispense directly to patient (injected IV forms a mass and can be lethal); abdominal SC injection - implant 4 small rods upper arm

MoA: mu partial agonist; maximal effect lower; ceiling effect; reduces opioid withdrawal and cravings, blunts effects of illicit opioid; bupe always wins
- naloxone not absorbed when taken orally, SL, buccally; therefore deters other routes/misuse

SE: constipation, withdrawal syndrome, sweating, vomiting, insominia, injection site rxn, implant site pain/irritation/swelling/falls out
CI: Sublocade must be directly dispensed to provider for admin as IV can result in harm/death
Precautions: respiratory depression and overdose (uncommon); most OD involve IV or concurrent depressants
- monitor liver function; can cause physical dependence; may cause sedation; may precipitate withdrawal; monitor DDIs

DDI: benzos, 3A4 inhibitors/inducers, antiretrovirals, serotenergic drugs

Recognizing opioid overdose
• Loss of consciousness • Unresponsive to outside stimuli • Breathing is very slow or stopped • Choking or gurgling sound • Fingers and lips turn bluish
Responding: check response (sternum rub), call 911, clear airway, perform rescue breathing, give naloxone
Naloxone: intranasal 4mg in one nostril; IM 2mg single dose, IV 0.4-2mg may repeat q2-3min
- works 2-5min; lasts 30-90min (may risk reoverdose) - caution naloxone will precipitate withdrawal

Opioid Withdrawal: Clinical Opioid Withdrawal Scale (COWS): scoring mild 5-12, moderate 13-24, moderately-severe 24-36, severe 36+
- methadone: must be done in OTP/inpatient; typically 20-30mg qday and taper over 6-10 days
- buprenorphine: in/outpatient; do not start until patient in moderate withdrawal; 4-16mg/d then tapered
- nonopioid: nausea (ondansetron, metoclopramide), diarrhea (loperamide), anxiety/irritability/sweating (clonidine), insomnia (DPH, trazodone), pain (NSAIDs)

Intoxication	Withdrawal	Overdose
Bradycardia	Tachycardia	Breathing shallow or absent
Hypotension	Hypertension	Bradycardia/hypotension
Hypothermia	Hyperthermia	Cold and clammy skin
Sedation	Insomnia	Pinpoint pupils
Meiosis (pinpoint pupils)	Mydriasis (enlarged pupils)	Nails and lips are blue
Euphoria	Anxiety	**Unresponsive**
Analgesia	Bone and muscle pain	
Constipation	Abdominal cramps, nausea, diarrhea	
Respiratory depression		

AUD
FDA-approved to treat AUD: acamprosate (1st-line), naltrexone (1st-line), disulfiram

acamprosate (Campral)
- GABA agonist/glutamate antagonist; restores balance of GABA/glutamate; reduces cravings
- 666mg (2x333mg DR tabs) three times daily, initiate ASAP following withdrawal; maintain if relapse
  - renal impairement: CrCl 30-50: 333mg tid; do not use first-line in mild-moderate renal disease

SE: diarrhea, insomnia, anxiety, depression
CI: severe renal impairment (CrCl ≤30ml/min)
Precautions: suicidal thinking/behavior; can cause CNS depression; caution renal

naltrexone
- opioid receptor antagonist; endogenous opioids involved in reinforcing effects of alcohol for which are reduced and also reduce cravings
- oral 50mg once daily (may require 100mg/d); ER IM 380mg (4mL) gluteal q4wk

disulfiram (Antabuse)
- aldehyde dehydrogenase inhibitor; blocks oxidation of alcohol causing buildup of acetaldehyde leading to disulfiram reaction
  - ingesting alcohol while on disulfiram can cause uncomfy sx: facial flushing, head/neck pain, vomiting, diaphoresis, chest pain, tachy, etc.
  - counsel about disguised sources of alcohol (mouthwash, OTCs)
  - disulfiram reaction can occur up to 14 days after taking
- 500mg qday for 1-2 weeks; do not administer until patient has abstained from alcohol for >12hrs
  - maintenance 125-500mg qday

SE: bitter/metallic taste, elevated liver enzymes, drowsiness/fatigue
CI: psychosis, severe MI or coronary occlusion; patients receiving alcohol, metronidazole, paraldehyde, alcohol-formulations
Precaution: hepatic impairment (hepatic cirrhosis or insufficiency)

Others: topiramate and gabapentin
- moderately effective at treating AUD (not FDA-approved); can trial after first-liners

Alcohol Intoxication and Withdrawal
withdrawal sx: anxiety, weakness, craving, insomnia, nightmares, confusion, tachy, HTN, sweating, NV, HA
- *hallucinations 12-48hr after last drink; seizures 6-48hr after last drink; delirium tremens 48-96hrs after last drink

Clinical Institute Withdrawal Assessment (CIWA-Ar): assess 10 sx using scale of 0-7
- mild 0-15 can treat outpatient >15 moderate-severe treated **inpatient**; also treat hx seizures/delirum tremens inpatient

Treatment
Benzos 1st-line: positive allosteric modulator at GABA-A receptors, enhance inhibitory effect of GABA; prevents seizures, reduce cravings/agitation
lorazepam: short HL, PO IV IM, glucuronidation
oxazepam: interm HL, PO, glucuronidation
chlordiazepoxide: long HL, PO, liver avoid if LFTs elevated
diazepam: long HL, PO IV, liver avoid if LFTs elevated
Example CIWA protocol - if CIWA >15 perisistent, patient is moderate risk; use fixed dose benzo taper; otherwise could use benzos based on sx
Fluids; vitamins: thiamine (B1) prevents Wernicke-Korsakoff syndrome (can lead to encephalopathy), give prior to glucose/dextrose; folic acid, phosphate, Mg

Summary
AUD
- acute intoxication (fatal): no treatment; supportive care, prevent withdrawal
- withdrawal (fatal): benzos (inpatient CIWA protocols), fluids, thiamine, folic acid, phosphate, Mg (if deficient)
- maintenance: naltrexone, acomprosate, disulfiram

OUD
- acute intoxication (fatal): no treatment; supportive care, watchful waiting
- overdose (fatal): naloxone
- withdrawal (non-fatal): opioid vs. non-opioid approach
- maintenance: methadone, buprenorphine/naloxone, naltrexone

Clinical Toxicology

https://www-uptodate-com.proxy.lib.ohio-state.edu/contents/general-approach-to-drug-poisoning-in-adults

• Familiarize yourself with overdose resources • Recognize symptoms of commonly overdosed medications • Recall the approach to treating a patient in a case of an overdose

• Identify the mechanism of action of discussed antidotes • Recommend treatment plans for the most common drug overdoses

• Know the number for the poison control center 1-800-222-1222 • Age matters • Be prepared to respond to common overdose scenarios based on your practice environment • Awareness and prevention is a MUST

Clinical Presentation

• Dependent on (amongst others) – Agent and route – Acute or chronic – Other medications (OTCs, herbals, supplements)

Diagnosis of Overdose

• History – Maybe unreliable with intentional overdoses – Look for pill bottles or a suicide note
• Physical examination – Mental status, vital signs, and pupillary examination
• Labs (toxicological)

Signs of Physiological Excitation

• CNS stimulation
• Increased BP Pulse Temperature Respiratory rate

Signs of Physiological Depression

• Depressed mental status
• Decreased BP Pulse Temperature Respiratory rate

Basic approach…

• Evaluate the situation – Is exposure possibly harmful?
• Collect information – Substance(s), formulation – Route – Time of incident (acute vs chronic) – Max amount of ingestion – Signs/symptoms – Weight
• Develop a treatment plan when necessary – Outpatient vs inpatient – Acute stabilization – Check (supportive care): Circulation, Airway patency, Breathing
• Management – Decontamination – Dialysis – Drug Antidotes – Enhanced elimination – *Supportive care
• Decontamination – Time is absorption – Methods: Eye - flush, GI - prevent absorption (activated charcoal); Skin - remove clothes and rinse with water

Antidotes

• "Treat the patient, not the poison"
• Appropriate use – No contraindications – Actual or predicted severity warrants use – Benefits >> risks
• Must consider the PK of the offending agent and the antidote

acetaminophen	N-acetyl cysteine
benzos	flumazenil
beta-blocker	glucagon
CCBs	calcium; insulin/glucose
digoxin	digoxin immune fab (Digibind)
iron	deferoxamine
opioids	naloxone
antidiabetics	octreotide
TCAs	sodium bicarbonate
warfarin	vitamin K

Pediatric Considerations…

• 6 and under – Exploratory ingestions • Syrup of Ipecac: *avoid, increase risk aspiration
• Increased susceptibility compared to adults – Inhaled toxins – Increased dermal exposure
• Rare – abuse by medical poisoning
• Common ingestions – Alcohols – Vitamins – Cosmetics – Pesticides – Topical products – Cleaning products – Cough/cold products
• Management – Supportive care – Decontamination (Activated charcoal) – Dialysis – Drug antidotes – Enhanced elimination

• Kids/Adolescents – Screen for acetaminophen ingestion/toxicity with intentional overdoses
• Value of urine drug screens – Possibly if unexplained symptoms
• Psychiatric assessment – Intentional overdose

One pill to kill

amitriptyline, baclofen, carbamazepine, clonidine, diltiazem, glyburide, opioids, propranolol, venlafaxine
camphor, essential oils, loperamide, salicylates, iron

APAP Toxicity
metabolized via 2E1 to N-acetyl-p-benzoquinone-imine (**NAPQI**); results in glutathione depletion
acute APAP: adults >7.5-10g children ≥150mg/kg
chronic APAP: adults >4g per day children: >90mg/kg per day

alcohol inhibits 2E1 in acute phase (hepatoprotective), but chronic use leads to 2E1 induced stage

Clinical presentation of APAP toxicity
Stage 1: first 2-24hr: asymptomatic, diaphoretic, NV, abdominal discomfort
Stage 2: days 1-3: increased AST/ALT, serum bilirubin, INR; latent phase, some upper quadrant tenderness
Stage 3: days 3-5: symptoms of hepatic injury including pain, jaundice, hypoglycemia, oliguiria, hepatic encephalopathy
Stage 4: days 4-14: recovery phase; patients that survive usually regain normal liver function/no long term issues
Additional labs: SCr, electolytes, transaminases, bilirubin, coag, glucose, urinalysis (hematuria/proteinuria)

Management of APAP toxicity
- predict hepatotoxicity using nomogram (modified Rumack-Matthew nomogram for acute ingestion only)
  - APAP blood samples >4 hrs after ingestion; plasma conc plotted above treatment line indicate hepatic damage = treatment
- sustained-release APAP delay in absorption, delay time to peak; need to check multiple levels 4 and 6hrs; may require further monitoring

Treatment: IV fluids, antiemetics, gastric lavage (not rec'd), supportive care, activated charcoal, N-acetylcysteine (NAC)
  - activated charcoal can be given if patient presents within 4 hours; best if 1hr after ingestion - no to cathartics, ipecac syrup

N-acetylcysteine (NAC): Gold standard treatment; use if above nomogram line
- most effective within 10 hours of ingestion (8% develop hepatotoxicity); 10-24hr window 30% hepatotox chance
  - may be started after 24hr in pt with fulminant hepatotox, serum APAP measurable, ingestion not recognized within 24hrs, and apparent liver toxicity

oral (Mucomyst 10-20%): 140mg/kg followed by 17 doses of 70mg/kg every 4 hours; total dose is 1330mg/kg over 72hrs SE: NV
  - may dc oral formulation after 36hr if APAP not detectable and AST/ALT levels normal
IV (Acetadote 20%): 150mg/kg over >60min; initial 50mg/kg infused over 4hrs, followed by second maint dose 100mg/kg over 16hrs; total 300mg/kg over 21h
  - IV 21hr similar outcomes to 72hr oral regimen; pediatric patients similar methods - monitor anaphylaxis

Activated Charcoal
- 1-2g/kg administered as aqueous slurry; adsorbs APAP; best if <1hr of ingestion; adsorbs up to 39% of oral NAC (stagger dosing with oral NAC if multiple doses)
- risk of aspiration (not rec'd for benzos)

Benzo Overdose
Sx: – Ataxia – Anxiety – Agitation – Dizziness – Drowsiness – Blurred vision– Slurred speech – Unresponsiveness – Altered mental status

Flumazenil (Romazicon)
- BZD antidote use controversial; only available BZD specific antidone; competitive BZD receptor antagonist
- very effective but precipitates seizures and disease/symptom return
- does not consistently reverse central resp depression; may experience resedation
SE: agitation, GI distress serious ADE: supraventricular arrhythmia and seizures
Avoid: hx seizures, coingestion of TCA, proconvulsants, head injury/cancer or metastatic disease to brain

Iron Overdose
nontoxic <20mg/kg moderate toxic 20-60mg/kg severely toxic >60mg/kg
Stage 1 (30min-6hr): NV, abd pain, diarrhea, hematemesis, hematochezia
Stage 2 (6-24hr): "apparent recovery"
Stage 3 (6-72hr): return of GI sx, shock, metabolic acidosis; coagulopathy, hepatic dysf, cardiomyopathy, renal failure possible
Stage 4 (12-96hr): liver damage and possibly failure
Stage 5 (2-8wk): "GI healing"; pyloric or proximal bowel scarring with possible obstruction
Treatment
- depends on amount; supportive care always
- severe admission: deferoxamine 15mg/kg/hr for up to 24 hrs
- GI decontamination in some circumstances

TCA Overdose
- supportive care (agitation), sodium bicarbonate (cardiac toxicity), isotonic saline (hypotension), benzos (agitation), physotigmine avoid

Beta-blocker Poisoning
- supportive care, IV boluses of isotonic fluid (hypotension), atropine (symptomatic bradycardia), IV dextrose (symptomatic hypoglycemia), others

<u>Dialysis</u>
Drug properties whether removed by dialysis: - small size <500 Da - low ppb - low Vd <1L/kg
- glimepiride high ppb - cannabinoids high Vd - phenobarbital will be removed by dialysis

Ceutics

Pure opioid agonist: As the dose increases, analgesia occurs in a log linear fashion, and the degree of analgesia is only limited by intolerable dose-related effects.
Opioids agonist/antagonist, or partial agonist (e.g.buprenorphine): Exhibit a ceiling of their analgesic effect. They can precipitate opioid withdrawal reactions.
Opioids antagonist (naloxone): Utility in the treatment of overdose.

diphenoxylate, loperamide: treatment of diarrhea. they slow GI motility and decrease secretion
- diphenoxylate typical opioid activity, combined with atropine to get Lomotil
- loperamide exported by PGP; drugs that inhibit PGP (verap) can lead to loperamide CNS SE

Routes - infusion pump - spinal delivery - local action - rectal - transmucosal - transdermal - Abuse Deterrent

<u>Knowledge Check</u>
Which pharmacokinetics considerations can you make regarding morphine metabolism?
- morphine metabolized to M6G (active, more potent) and M3G (no analgesic, responsible for SE of morphine)
- accumulation of such metabolites in renal insufficiency or high doses (>300mg/day)
- routes of admin that bypass first-pass (IV/SC) can have less SE as the morphine to metabolite ratio is higher

Why should MAOi and meperidine combination be avoided?
- MAOi inhibit meperidine metabolism = higher mepridine concentration
- meperidine inhibits serotonin reuptake, can induce serotonin syndrome (can result with coadmin of TCA or SSRI too)

Why buprenorphine can antagonize fentanyl-induced respiratory depression without reversing opioid pain relief?
- partial agonist of MOR, exerts limited intrinsic activity when administered
- when given with fentanyl, it can control respiratory depression, while partial activity of MOR can still maintain pain relief
- can also induce symptoms of abstinence in patients who have been receiving agonists for weeks

What is intended with patient-controlled analgesia (PCA)?
- PCA assumed to be on-demand, intermittent, IV admin under patient control
- alternative routes epideral, peripheral nerve catheter, transdermal PCA
- advantages over continuous infusion: superior analgesia, patient satisfaction, fewer SE

What is an opioid abuse deterrent formulation?
- intent to reduce attractiveness; limits bioavail, prevent admin through other routes, making abuse of manipulated product less rewarding/attractive
- primary approach: physical barrier, viscosity management, solubility modification, sorption processes
  - OxyContin “intact technology” which is resistant to mechanical tampering and chemical extraction by forming a gel
- secondary approach: combining active opioid with antagonists or enzyme inhibitors
  - Embeda combo of morphine and naltrexone. Naltrexone is released and blocks effect of morphine if pills are crushed
- tertiary approach: aversive agents; combination of opioid with substances that induce unpleasant effects when taken in large qty
  - Acurox (oxycodone/niacin) causes flushing when consumed in high doses
  - Lomotil (diphenoxylate/atropine)
- mixed approach: viscosity management and aversive ingredient

Musculoskeletal Pharmacology

I. Inflammation - Inflammatory Response - Eicosanoids II. Glucocorticoids III. NSAIDs IV. RA V. Osteoarthritis VI. Gout VII. Osteoporosis

Study Guide
Remember, if something is labeled "FYI" in the notes, you do not have to memorize it.

Know what inflammation is and the evolution of acute inflammation over time.
Know the concept of onset and resolution and the scheme on p4

Know the key points for the cytokines on p8-10.

Know the overall Prostaglandin system summary diagram and mediator characteristics on p18
Know the generalities about Phospholipase A2 (p13) and COX1, COX2, and specific Prostaglandin synthases on p20
Know the main actions of prostacyclin (PGI2) thromboxane (TXA2) and prostaglandin E2, p21
You should be able to figure out how this explains some NSAID actions and side effects.

Know p23, 24, 25.

Regarding analgesic effects of NSAIDs, just know that prostaglandins made via COX and Synthases can sensitize nociceptors, and the main point on p27.
Regarding Tylenol, you just need to know the main point on p30

For the other NSAIDs, remember analgesia, antipyretic, anti-inflammatory actions and put that together with a use in arthritis etc

Know all about aspirin from p34-37
Regarding COX1 vs COX2 selectivity, just know that Celecoxib is COX2 selective and that low dose aspirin is COX1-selective.

Know the pathology and goals of RA treatment, p43-44
Know that hydroxychloroquine, p46, has several anti-inflammatory effects useful in RA and is more well-tolerated than methotrexate for milder cases
Regardless of knowledge about Methotrexate affecting inflammatory cells, know biochemical actions and the ability to increase adenosine, and toxicities, p47-50

Know the Biological DMARDs for RA on p54 and in the list on the next page.
Know the mechanisms and common toxicity of these agents, p55-62.

Regarding cytokine signaling, just know the receptors that can activate inflammatory gene transcription.
For IL6, be able to differentiate the mechanism of antibodies and JAK inhibitors.

Know the general management strategy for osteoarthritis, p65

Know about gout, p66-67, and colchicine p68.
For drugs in the list at the end, from notes pages 68-71, know the mechanism and the problem of acute drug-induced flare in gout.

<u>Osteoporosis</u>
Know the role of osteoblasts, osteocytes and osteoclasts
Know the basics of the remodeling cycle on p73 and the role of disruptions in osteoporosis
Know RANK, RANKL, OPG, Sclerostin, and the idea of intercommunication between osteoclasts and osteoblasts, and the therapeutic consequences of it, p74-75

Know the Main Net Effects of PTH, Calcitriol and Calcitonin on p80

Know the bisphosphonate information on p83-85, Denosumab and Romosozumab, p86-87, PTH analogs and calcitonin, p88-89

Know the actions of estrogen/SERMs p90 and the bit about raloxifene (Evista), p91

Know if the treatment can cause hypocalcemia or hypercalcemia.

Know if a treatment can cause osteonecrosis of the jaw and sensitivity of femur to breakage.

Basically, all the agents reduce osteoclast activity, some causing apoptosis, except for Romosozumab and PTH analogs, which increase osteoblast activity.

I will not ask about: Diclofenac, Meloxicam, Meclofenamate, Mefenamic acid, Nabumetone
Other TNF antibodies: Golimumab (Simponi), Certolizumab (Cimzi), Infliximab (Remicade)
Or other non-biologic DMARDs: Leflunomide (Arava)

Anti-inflammatory Agents

A. Glucocorticoids: Prednisone (Deltasone), Methylprednisolone (Medrol), Prednisolone (Orapred)

B. Non-steroidal anti-inflammatory drugs – NSAIDS
1. Para-Aminophenol Derivatives: Acetaminophen
2. Salicylates: Aspirin
3. Propionic Acids: Ibuprofen, Naproxen
4. Acetic Acid Derivatives: Diclofenac; Etodolac, Indomethacin, Sulindac, Tolmetin
5. Oxicams (Enolic Acids): Meloxicam (Mobic)
6. Fenamates: Meclofenamate, Mefenamic acid
7. Nonacidic napthylalkanone: Nabumetone
8. Intentionally Selective COX-2 Inhibitor: Celecoxib (Celebrex)

C. Non-biological Disease Modifying Anti-Rheumatic Drugs (DMARDs): Hydroxychloroquine (Plaquenil), Methotrexate (Rheumatrex), Leflunomide (Arava)
Others: Sulfasalazine, Azathioprine, Gold, Cyclosporine, Penicillamine, Cyclophosphamide

D. Biological DMARDs = Cytokine and inflammatory cell blockers
1. Anti-TNF-αtherapy: Etanercept (Enbrel), Infliximab (Remicade), Adalimumab (Humira), Golimumab (Simponi), Certolizumab (Cimzi)
2. Anti-IL-1 therapy: Anakinra (Kineret)
3. Anti IL-6 therapy: Tocilizumab (Actemra), Sarilumab (Kevzara)
4. Janus Kinase Inhibitors – block cytokine signaling: Tofacitinib (Xeljanz), Baricitinib (Olumiant), Upadacitinib (Rinvoq)
5. B-cell depletion: Rituximab (Rituxan)
6. Disrupt T-cell activation: Abatacept (Orencia)

Osteoporosis

1. Discuss general pathophysiology and potential consequences
2. Identify screening and diagnostic criteria
3. Determine evidence based therapeutic interventions
4. Distinguish between potential pharmaceutical interventions
5. Identify appropriate monitoring and clinical pearls for specific interventions
6. Apply treatment algorithm to patient scenarios

Estrogen in bone remodeling
A DECREASE (deficiency) in estrogen is associated with an INCREASE in:
• Bone cytokines • RANK-L expression • Osteoclast expression and longevity • Osteoblast apoptosis

OSTEOPOROTIC FRACTURE
- after fracture: decreased QoL, decreased mobility, loss of independence, corrective surgery; chronic pain, DVT/PE

Screening (risk factors: Hx of fracture after 50yo; aggravating condition (RA); chornic medication use (glucocorticoids)
women ≥65yo postmenopausal women >50yo women in menstrual transition Men ≥ 70yo men 50-69yo with risk factors any adult with risk factors

In the absence of a fragility fracture, BMD assessment by DXA is the standard test to diagnose osteoporosis
DEXA (DXA) "scan" (Dual Energy X-ray Absorptiometry): StDeviation away; can improve; take every 1-2 years
• Gold standard • Measures bone density • Generates a T-score • T-score ≠ Z-score • Z-score is "matched" to age, sex, ethnicity
- exponential relationship between decreasing bone mass/density and increase incidence of fractures
T-score: Normal >-1.0 Low bone mass (osteopenia) -1.0 to -2.5 Osteoporosis <-2.5 Severe (established) osteoporosis -2.5 with fracture

2020 AACE Diagnosis criteria:
1. T-score -2.5 or below in the lumbar spine, femoral neck, totalproximal femur, or 1/3 radius
2. Low-trauma spine or hip fracture (regardless of bone mineral density)
3. T-score between -1.0 to -2.5 and a fragility fracture of proximal humerus, pelvis, or distal forearm
4. T-score between -1.0 to -2.5 and high FRAX® fracture probability based on country-specific thresholds (>20%)

HIGH-RISK • Diagnosis with osteoporosis, but not at very high fracture risk
VERY HIGH-RISK • Recent fracture (12 mo) • Fracture on OP treatment • Multiple fracture history • T score <-3.0 • High risk of falls • High FRAX score

<u>Prevention</u>
<u>Calcium</u> - age 19-50yo 1000mg/day - women >51yo, men >71yo 1200mg/day - take in divided doses 600mg bid
average adult consumes 600-700 mg/day in Ca from foods include dairy, fortified orange juice, broccoli, soybeans; thus requires supplementation; divide doses max 1200mg/day
carbonate (take with **food**/need acid) 40% elemental calcium = 200mg/500mg Ca tablet citrate 21% elemental 105mg/500mg tablet
<u>Vitamin D</u> - deficiency 50000iu weekly for 8-12 weeks - adult <50yo 400-800iu daily - adult >50yo 800-1000iu daily
essential for calcium absorption, measured by 25-OH-D levels: deficient <20ng/ml, optimal >30ng/ml, therapeutic 30-50ng/ml

Nonpharm
weight bearing: promotoes bone strength, muscles work against gravity; lift weights, resistance, bands
muscle strengthening: promotes strength/coordination, prevents falls, target core muscles to support back and spine
- caution: avoid forward flexion of spine or bending forward from waist, twisting/jerking spine, high-impact exercise
nicotine: interferes with bone health and healing; causes vasoconstriction and oxygen deprivation; increased healing time (60% more time in healing)
alcohol: increased fall risk, decreased bone mineralization; increased oxidative stress
fall prevention: poor vision, balance, depression, dehydration, arrhythmia, anxiety, OH, **medications**, muscle atrophy, diminished cognition, decreased proprioception

Causes of Secondary Osteoporosis: T1DM T2DM, hyperthyroidism, pregnancy, alcoholism, anorexia, chronic liver disease, Crohns, celiac, GI bypass, TPN glucocorticoids, immunosuppressants/chemo, AEDs (carbmaz, phenobarbital, phenytoin), aromatase inhibitors, GnRH agonists/antagonists, heparin, lithium, PPI, SGLT2, TZD, SSRI

Treatment Options

Anti-resportive: supportive osteoclasts, slow bone resorption, decrease fracture risk, stabilize bone architecture

- bisphosphonates - RANKL inhibitor: denosunamb (Prolia) - estrogen replacement therapy - estrogen agonist/antagonist - calcitonin

Anabolic agents: stimulate bone formation (osteoblasts), increase BMD, decrease fracture risk

- parathyroid analog: teriparatide (Forteo), abaloparatide (Tymlos) - sclerostin inhibitor: romosozumab (Evenity)

Bisphosphonates 1st-line treatment

Bisphosphonates target osteoclasts: alendronate PO, risedronate PO, ibandronate PO/IV, zoledronic acid IV; others (etidronate, pamidronate, tiludronate treat other bone diseases)

1. drug concentrates at remodeling sites in the Ca-Phosphate bone matrix and inhibit bone resorption by osteoclasts
2. after bone remodeling cycle is complete, acid environment created by osteoclasts releases bisphosphonates from matrix; causes osteoclast apoptosis, reducing their number

Indications

1. postmenopausal prevention/treatment 2. increase bone mass in men with osteoporosis 3. prophylaxis in patient taking glucocorticoids 4. prevention hx low trauma hip frac

		% reduction in new fractures over 3yr vertebral hip non-vertebral	
alendronate PO 1 2 avoid CrCl <35	prevention 5mg qd or 35mg qwk treatment 10mg qd or 70mg qwk (comes with Vit D3)	44% 40% 17%	
risedronate PO 1 2 3 avoid CrCl <30	prevention and treatment 5mg qd or 35mg qwk or 150mg qmo (or 75mg 2d/mo)	36% 26% 20%	
ibandronate PO/IV 1 avoid CrCl <30	prevention 150mg qmo treatment 150mg qmo or 3mg IV q3mo	31% 0% 0%	
zoledronate IV 1 2 3 4 avoid CrCl <35	prevention 5mg IV over 15min q2yr treatment 5mg IV over 15min q1yr	56% 42% 18%	

Monitoring

- renal function
- calcium
- resorption markers (↓ over time): serum C-telopeptide (CTX), urinary N-telopeptide (NTX)
- formation markers (↑ over time): serum bone specific alkaline phosphatase (BSAP), osteocalcin (OC), aminoterminal propeptide of procollagen (PINP)

Side Effects

Common: gastric ulceration, eye inflammation, flu-like reaction (IV specific), hypocalcemia

Rare: osteonecrosis of jaw (high doses IV or use of PO >5yrs), atypical fractures (unusual femur fractures with sx of aching pain in hip)

Counseling

- poor bioavailability
- take with 6-8 oz of water AND on empty stomach
- remain in an upright position for 30-60 minutes post administration

*"Take first thing in the **morning**, on an empty stomach, with a full glass of water and remain upright for 30 minutes after taking; do not lie back down after you take this medication."*

- should be used with appropriate calcium and vitamin D intake

To discontinue or not? Treament can always be resumed if resorption/formation markers indicate a need

Discontinue: most patients (high risk) can d/c treatment after: zoledronate 3 years, others 5 years (very long HL)

Keep treatment: BMD <-2% high fracture risk, or previous fracture; very high risk patients: zoledronate 6 years, others 6-10 years

RANKL inhibitor

denosumab (Prolia) 60mg SQ q6mo; no renal adj

MoA: antibody that neutralizes RANKL like OPG, to stimulate bone formation by reducing osteoclast activation

Indication: postmenopausal TREATMENT

Monitor: SCr, calcium, phosphorus, magnesium, resorption markers (within 3 days it works), BMD

Side effects: upper GI complaints, skin infections, rash, osteonecrosis of jaw, atypical fractures

Counseling: refridgeration, rotate inj site, do not shake; used with calcium and vitamin D; rapid bone loss when d/c (transition onto diff anti-resorption drug)

Effectiveness vs. ibandronate: decrease resorption markers, increase BMD

Estrogen replacement:

Premarin PO, Estrace PO, Climara patch

MoA: act on osteoblast progenitors to reduce their production of osteoclast activating cytokines; represses osteoclasts relative to osteoblasts to maintain bones - inhibits production of RANKL by osteoblasts - increases OPG (the RANKL inhibitor)

Indication: postmenopausal PREVENTION

Risks: MI, stroke, breast cancer, DVT/PE - age 50-59yo decreased total mortality, but increase in >60yo

Who's for: <60yo, <10yr past menopause; low DVT risk; failed bisphosphonates/denosumab; estrogen for other benefit (hot flashes), no hx MI, stroke, BC

Counseling: avoid grapefruit PO, monitor MI, stroke, clot; no renal adjustments; take with calcium vitamin D intake

Estrogen agonist/antagonist

raloxifene (Evista) 60mg qday; no renal adj

Indication: postmenopausal PREVENTION/TREATMENT; decreases risk of invasive BC in postmenopausal women

Side effects: DVT/PE, stroke, athralgia, bronchitis, leg cramps, hot flashes

Counseling: do not use with cholestyramine/colestipol; s/s clot, may decrease cholesterol/LDL; take with calcium vitamin D intake

bazedoxifene and conjugated estrogens (Duavee) 0.45/20mg qday

Indication: postmenopausal PREVENTION; treatment of hot flashes in menopause

Side effects: ND, dizziness, neck pain, contains estrogen (consider risks)

Counseling: short course of therapy; limit to patients with most significant risk of osteoporosis (usually pt who have osteopenia/high risk)

Calcitonin

calcitonin (Miacalcin, Fortical) 200 IU intranasally/SQ qday

Indication: postmenopausal TREATMENT (at least 5yr post-menopausal)

Side effects: salmon product (allergy?); cancer? intranasal: rhinitis, epistaxis, back pain SQ: abd pain, rash, itch, fever

Counseling: intranasal switch nostril every other day, discard bottle after 30 doses (1 mo); SQ rotate inj site; take with calcium and vitamin D3

Monitor: risk of hypocalcemia (total 8.6-10.5mg/dl; ionized 4.6-5.3mg/dl); hypocalcemia mild has no sx; severe hypo can cause lethargy, seizures, arrest

Parathyroid analogs

teriparatide (Forteo) 20 mcg SQ qday for max 18-24mo

Indication: osteoporosis TREATMENT in men and women at high risk of fracture; treatment in osteoporosis taking glucocorticoids

Side effects: upper GI sx, HA, hypercalcemia, leg cramp, N, dizziness, osteosarcoma?

Counseling: avoid use in osteosarcoma, not to be used longer than 18-24mo, rapid bone loss when d/c (these drugs increase bone growth), no renal adj

Monitor: calcium, phosphorus, formation/resorption markers, effects 'fade' within one year of therapy

abaloparatide (Tymlos) 80 mcg SQ qday

Indication: postmenopausal TREATMENT

Side effects: dizziness, N, HA, OH, hypercalcemia, kidney stones

Sclerostin inhibitor

romosozumab (Evenity) 210 SQ qmo for max 1 year

MoA: antibody that neutralizes sclerostin, an osteoblast inhibitor; thereby increases osteoblast activity

Indication: postmenopausal TREATMENT

Side effects: HA, joint pain, cardiac events (MI, stroke), hypersensitivity, hypocalcemia, osteonecrosis of jaw, atypical fractures

Nahata

Table 2. Differentiation among Various Forms of Arthritis.*

Variable	Psoriatic Arthritis	Rheumatoid Arthritis	Gout	Osteoarthritis
Joint distribution at onset	Asymmetric	Symmetric	Asymmetric	Asymmetric
No. of affected joints	Oligoarticular	Polyarticular	Monoarticular or oligo-articular	Monoarticular or oligo-articular
Sites of hands or feet involved	Distal	Proximal	Distal	Distal
Areas involved	All joints of a digit	Same joint across digits	Usually monoarticular	Same joints across digits
Tenderness (kg on a dolorimeter)	7	4	NA	NA
Purplish discoloration	Yes	No	Yes	No
Spinal involvement	Common	Uncommon	Absent	Noninflammatory
Sacroiliitis	Common	Absent	Absent	Absent

Rheumatoid Arthritis

https://www.uptodate.com/contents/table-of-contents/rheumatology/rheumatoid-arthritis

Etiology: exact unknown; autoimmune or infectious (proliferation of synovial macrophages/fibroblasts)
- ↑ proinflam cytokines (TNF, IL-1, IL-6) - soft tissue swelling = joint space narrowing - bone erosing = joint deformity/destruction

Affects proximal interphalangeal (PIP), metacarpophalangeal (MCP) joints of fingers, metatarsophalangeal (MTP) feet, wrists, knees, ankle, hip, shoulder, spine
Clinical features: joint pain, tenderness, swelling; usually symmetrical distribution; prolonged joint stiffness in AM >1hr; fatigue, malaise, wt loss
- lower range of motion and joint function - 10-35% have rheumatoid nodule (growth of subcutaneous tissue in or around joints)

Lab/Procedures: radiograph, CBC (anemia of chronic disease), erythrocyte, sedimentation rate, C-reaction protein, Rheumatoid factor, Anti-CCP Ab, synovial fluid analysis, antinuclear antibody (ANA)
Nonpharm: rest/exercise/physical therapy; heat to decrease stiffness; assistive devices (cane, brace, walker); emotional; complementary/alternative
Pharmacology
NSAIDs: analgesic/antiinflam but no effect on disease progression
DMARDs: no immediate analgesic effect but can control symptoms and delay disease progression
Corticosteroids: rapid relief and systemic illness but can cause severe toxicity with chronic use
Combination of above

American College of Rheumatology Criteria for Improvement
A. improvement in tender/swollen joint counts AND
B. 3 of 5: improvement in patients global assessment, MDs global assessment, pain, degree of disability, level of acute phase reactants
- ACR50 means 50% improvement in A&B

<u>NSAIDs</u>
- relatively selective preferential for COX-2: meloxicam, nabumetone, etodolac, diclofenac
- selective for COX-2: celecoxib

advantage?

Psoriatic Arthritis

https://www.uptodate.com/contents/treatment-of-psoriatic-arthritis

Gout and Hyperuricemia

Gout: colchicine (Colcrys), allopurinol (Zyloprim), febuxostat (Uloric), pegloticase (Uricase), probenecid (Benemid), lesinurad (Zurampic)

Intro
•Acute gout characterized by sudden onset of severe acute monoarticular arthritis in peripheral joints
•Involves deposition of monosodium urate crystal in and around joint cartilage (tophi)

Prevalence
•8.3 million affected in US (more visits)
•Most common type of inflammatory arthritis
•Men 2-3 times more affected than women <65 yo
•No gender difference and can be polyarticular in those >65 yr of age

Implications
• 75% recur in 1-2 years after acute attack
• Severe pain with acute attack
• Deformity, soft tissue damage and joint destruction with chronic gout
• Can lead to nephrolithiasis and kidney damage with chronic gout

Etiology/Pathophys
• Humans lack uricase to convert uric acid to soluble products
• Overproduction and/or underexcretion can lead to hyperuricemia

Risk factors
•Hyperuricemia (≥ 6.8 mg/dL) •Obesity •Alcohol •Hypertension •Kidney disease •Dehydration •Neoplastic diseases
•Drugs: Thiazides, low dose salicylates, niacin, etc.

Affected areas
•First metatarsophalangeal joint (great toe) •Insteps •Ankle •Knee •Elbow •Wrist •Fingers •Hip and shoulder (rare)

Clinical Features
•60-90% of first attack→monoarticular
•Polyarticular with disease progression
•Sudden onset of pain, warmth, tenderness, swelling, erythema
•Decreased range of motion with progression
•Presence of tophi
•Sodium urate crystals in and around joints

Lab data/Procedures
•Serum uric acid
•>8 mg% indicates significant hyperuricemia
•Urinary uric acid
•<800 mg/24h indicates underexcretion
•Radiography; other imaging techniques
•Synovial fluid analysis
•Erythrocyte sedimentation rate
•C-reactive protein

Treatment of Acute Gout
•Oral colchicine or an NSAID (corticosteroid if needed) if mild-moderate
•Combination therapy if severe
•Use alternate drug if inadequate Tx
•Duration: 5-7 days
•Use topical ice as needed

Colchicine in Acute Gout
•Selective for relieving gouty pain (useful in diagnosis)
•1.2 mg PO then 0.6 mg at 1-2 hours
•Then 0.6 mg QD or BID until resolution
•25% have N/V, diarrhea, cramps
•Avoid or reduce colchicine dose with P-gp and CYP3A4 inhibitors

NSAIDs for Acute Gout
•Naproxen 750 mg x 1 dose, 500 mg at 8h, then 250 mg TID x 2-3 days and taper
•Ibuprofen 800 mg QID day 1, then taper as needed for pain
•Indomethacin 50 mg PO TID x 2-3 days and then taper over the next 2-4 days
•Sulindac 200 mg BID or ketoprofen 75 mg QID could also be used

Corticosteroids
•Triamcinolone intraarticular injection 10-40 mg for a large joint and 5-10 mg for small joint
•Prednisone 0.5 mg/kg PO x 1-2 days; taper by 5 mg each day over a week for polyarticular disease
•Add NSAID if needed

Treatment of Hyperuricemia
•Patients may have 2 or more episodes of acute gout/year
•Goal is to control tophi, stones, joint erosion and prevent renal failure
•Goals: Decrease symptoms of attacks, Decrease recurrent attacks, Reduce serum urate
•Target: less than 6 mg%
•Asymptomatic hyperuricemia may be treated in certain patients

Allopurinol
•Lowers production of uric acid by inhibition of xanthine oxidase
•100 mg once daily initially; 200-300 mg/d maintenance (Max. 800 mg/d)
•Dose based on renal function: 300 mg for normal, 200 mg for creatinine clearance <60 mL/min, 100 mg for 30 mL/min
•ADRs: rash (HLA-B*5801 test?), GI; serious interaction with azathioprine or mercaptopurine

Febuxostat (Uloric)
•Selective inhibitor of xanthine oxidase
•Start 40 mg PO once daily; increase to 80 mg once daily to achieve UA <6 mg%
•No dose adjustment in mild to moderate renal or hepatic disease
•Black Box Warning for increased CV death & mortality compared to allopurinol
•ADRs: GI, liver enzymes, rash, arthralgia; all cause mortality and cardiovascular mortality higher than allopurinol (NEJM 2018)

Lesinurad (Zurampic) Tablets as Add-on Treatment
•Inhibits function of transporter proteins (URAT1) involved in uric acid reabsorption in kidney
•Indicated for patients not reaching target UA levels on XOI alone
•200 mg PO QAM plus XOI with food/water
•ADRs: Headache, influenza, increased SCr, GI reflux
•Warning: Acute kidney failure (more common without XOI and at higher than approved doses)

Lesinurad with Allopurinol (Duzallo)
•Indicated when allopurinol alone not effective in reaching targted UA level
•Tablets containing 200 mg each; and 200 mg lesinurad/300 mg allopurinol
•One tablet each morning with food/water
•Drink 2 liters (68oz) fluid daily to stay hydrated

Pegloticase (Krystexxa) for Chronic Gout
•A recombinant uricase converts uric acid to allantoin
•Used in patients refractory to or unable to take conventional therapy; Not asymptomatic hyperuricemia
•8 mg IV 2 hour infusion Q 2 weeks; Premedicated with antihistamine and corticosteriod
•Monitor uric acid conc. before each dose
•Approved with REMS; Black Box Warning for anaphylaxis and infusion reactions

Uricosuric Drugs
•↓ Reabsorption of uric acid if underexcretion present
•CrCl >60 ml/min, no nephrolithiasis
•Probenecid 250 mg BID (Max 2 g/d)

- Sulfinpyrazone 50 mg BID
- May be added to uric acid lowering drug
- ADRs: GI, rash, uric acid precipitation, renal calculi so start low

Multiple Sclerosis

1. Identify the clinical presentation of multiple sclerosis (MS)
2. Select the most appropriate disease modifying treatment for a patient with MS
3. Recommend appropriate treatment for the symptoms associated with MS
4. Develop an an appropriate monitoring plan for common MS treatments
5. List counseling points for common MS treatments

https://accesspharmacy-mhmedical-com.proxy.lib.ohio-state.edu/content.aspx?bookid=2577&sectionid=231921409
https://www-uptodate-com.proxy.lib.ohio-state.edu/contents/search?search=rrms

Clinical Presentation

- CNS autoimmune disorder characterized by demyelination and axonal damage
  - –Progressive non-reversible disease
  - –Exacerbations/relapses
  - –Varying clinical presentations
    - primary sx: symptoms that arise directly from the disease state itself from the external axonal damage
    - secondary sx: associated with primary; 7x more likely risk of attempting suicide
    - tertriary sx (invisible): decrease functional impairment on the job or psychological problems that result from the toll of the disease itself
- Four basic subtypes:
  - –**Relapsing-remitting**: characterized by clearly defined attacks (aka relapses, flares, exacerbations) with full or incomplete recovery
    - sx last >24hrs and separated by another attack by >30days; 85% of patients
    - increase in symptom severity with each new attack
    - residual symptoms between attacks
      - Expanded Disability Status Scale (EDSS) and functional systems
  - –Secondary progressive: characterized by an initial relapsing-remitting MS disease course followed by gradual worsening with or without occasional relapses, minor remissions, and plateaus
  - –Primary progressive: characterized by progressive accumulation of disability from disease onset with occasional plateaus, temporary minor improvements, acute relapses still consistent with the defn
  - –Progressive relapsing
- Exacerbations
  - –New symptoms lasting >24 hours with 30 day separation from other new symptoms
  - –Risk factors • Heat • Stress • Anemia • Infections • Sleep deprivation • malnutrition, organ dysf, exertion

Patient Evaluation

- MS classification
- Disease severity
  - poor prognosis: >40yo, Male, motor/cerebellar sx, early disability, high frequency exacerbations, slow first recovery
- Exacerbations
- Treatment
  - –Disease Modifying Therapy (DMT)
  - –Symptomatic
  - –Counseling points
- Monitoring

Treatment Goal

- Maintenance–Slow disease course and minimize long-term disability
- Exacerbation–Lessen duration and severity of exacerbation
- Symptoms–Maintain and improve QOL

Treatment Approach

- No standard guidelines–Large variability among clinicians
  - two basic approaches: induction and escalation
  - those not treated with DMT relapse every 6 months; those that are on DMT relapse every 2-5 years
- Consider goals and thoughts of patients
  - –Route of administration
  - –Side effects
  - –Adherence
- Medication that offers clinical benefit with the least amount of risk – individualize for patient

Assess for Nonadherence

- High rates with treatment due to:
  - –Cost
  - –Depression
  - –Adverse effects
  - –Perceived lack of benefits
  - –Undesirable route of administration

Treatment Algorithm

Exacerbations

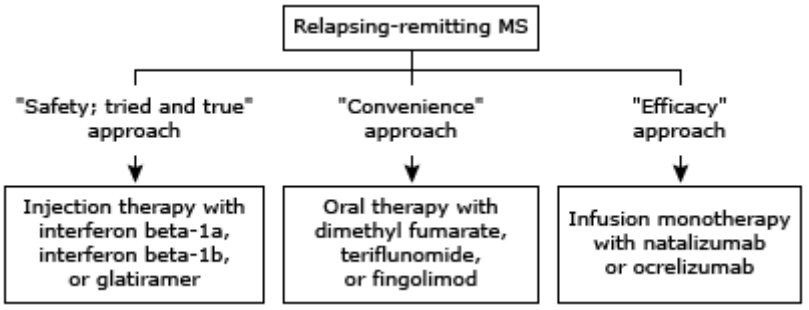
- To treat or not to treat?
  - –Patient expectations
  - –Past success/lack of success
  - –Predicted path of recovery: disability over time will occur due to the accumulative effects of these exacerbations
- IV high dose corticosteroid
  - –**Methylprednisolone IV 500-1,000 mg/day x 3-10 days** - decrease edema around the area of the demyelination, which can help improve symptoms
    - Side effects? mental status changes, increased susceptibility to infection, gastric disturbance are potential complications
      - Psychiatric side effects can include increased depressive, manic, and hypomanic symptoms
      - To mitigate these side effects, we suggest the prophylactic use of a proton pump inhibitor in the morning and low-dose clonazepam at night while on glucocorticoid treatment

Disease-Modifying Therapy (DMT)

- Important considerations
  - –Understanding of disease severity
  - –Current knowledge of MOA of DMTs
  - –Adverse effects (tolerability)
  - –Long term safety considerations
- Escalation vs. Induction
  - escalation: RRMS, mild disease, better prognostic factors; start with safer/milder agent, only use more risky when failed first-line
  - induction: patients with more severe disease, poor prognosis; use higher risk agents, 2nd-gen

- Escalation and 1st generation agents
  - –Four INF agents: Interferon-β_{1a} IM (Avonex) Interferon-β_{1a} SQ (Rebif) Interferon-β_{1b} SQ (Betaseron, Extavia) Pegylated Interferon-β_{1a} SQ (Plegridy)
  - –Glatiramer acetate (Copaxone, Glatopa)
- Time to onset is approximately 1 to 2 years

- Second generation agents
  - –Varying MOA and Efficacy: either immunomodulatory or immunosuppressive
    - Teriflunomide PO (Aubagio)
    - Fingolimod PO (Gilenya)
    - Dimethyl fumarate PO (Tecfidera)
    - Natalizumab IV (Tysabri)
    - Alemtuzumab IV (Lemtrada)
    - Ocrelizumab IV (Ocrevus)
    - Mitoxantrone IV (Novantrone)
- Medication considerations
  - –Route
  - –Pretesting
  - –Dosing frequency
  - –Adverse effects
  - –Monitoring
- Possible to see interpatient and intrapatient variability
- Very challenging to define clinical failure



	Pretest	Adverse Effects	Monitor	Comments
interferon-β_{1a} (Rebif, Avonex) interferon- β_{1b} (Betaseron) low—SQ/IM	LFTs CBC HCG	HA, spacticity, depression, lymphopenia, hepatotox, flu-like sx --inj site rxn	sx CBC LFTs QoL MRI TSH	avoid severe untreated depression
glatiramer acetate (Copaxone) low—SQ	N/a	urticaria, infection, lipoatrophy, chest tightness, hypersensitivity --inj site rxn	sx QoL MRI tissue necrosis	preg cat B
teriflunomide (Aubagio) low—PO	TB LFTs CBC HCG	SJS, ND, alopecia, neuropathy, teratogenicity, hepatotox	sx CBC LFTs QoL MR TB HCG	avoid hepatic impair preg cat X
dimethyl fumarate (Tecfidera) med—PO	LFTs CBC HCG	**PML**, rash, N, flushing, pruritus, lymphopenia, GI discomfort	sx CBC LFTs QoL MRI	taking with food limits flushing
fingolimod (Gilenya) med—PO	ECG CBC HCG LFTs, OCT (optimal coherence tomography)	HA, HTN, HSV, **PML**, bradycardia, lymphopenia, transaminitis, macular edema, dermatologic cancer	sx CBC LFTs QoL MRI ECG OCT	REMS program; requires 1st dose obs avoid class I/III antiarrythmias and cardiac disease mindful of DDI/ vaccines
natalizumab (Tysabri) high—IV q4wk	CBC HCG LFT **JCV**	HA, HSV, **PML**, arthralgia, depression, encephalitis, hepatotox --infusion rxns	sx CBC LFTs QoL MRI	REMS program *natalizumab neutralizing antibodies after 6mo
alemtuzumab (Lemtrada) high—IV	UA TB CBC SCr LFTs TSH HIV HCG HSV	rash, fatigue, N, HA, thyroid disease --infusion rxns	sx CBC QoL MRI UA TSH infections, bone marrow suppression, autoimmune disorders	REMS program; premed methylpred strokes (rare) very $$$

PML, progressive multifocal leukoencephalopathy (monitored via MRI)
- confusion, depression, trouble with memory, behavioral changes, change in strength on one side is greater than the other, trouble speaking, change in balance, vision changes

www.uptodate.com/contents/disease-modifying-therapies-for-multiple-sclerosis-pharmacology-administration-and-adverse-effects
Newer Approved Therapies
• Ocrelizumab (Ocrevus): March 2017 –Relapsing and primary progressive (RRMS, PPMS) **PML**
• Siponimod (Mayzent): March 2019 –Relapsing forms
• Ofatumumab (Kesimpta): August 2020 –Adults with clinically isolated syndrome, relapsing-remitting disease, and active secondary-progressive disease
• Diroximel fumarate (Vumerity): Late 2019 –CIS, RRMS, SPMS (bioequivalent to dimethyl fumarate; metabolizes to active monomethyl fumarate)
• Monomethyl Fumarate (Bafiertam): April 2020 –CIS, RRMS
MS CAM Oral cannabis extract (A), synthetic THC (B) for symptoms of spasticity and pain in RRMS, SPMS, PPMS, MSU

<u>Symptom Management</u>
• Key to maintaining and improving QOL
• Many symptoms, focus on just a few –Pain **–Fatigue** **–Spasticity** –Cognitive –Depression –Sensory symptoms –Bladder and bowel symptoms

Spasticity • Seen later in disease • Legs > arms; Increase risk for falls • Balance treatment to avoid decreasing muscle tone too much
Spasticity Treatment
• Baclofen
  –Avoid abrupt withdrawal
  –Intrathecal formulation available
  –Potential dose adjustment with renal impairment
• Tizanidine
  –Potential risk for drug interactions
  –Monitor for hypotension (structurally similar to clonidine)
• Diazepam
  –Abuse potential
  –Slow titration – avoid abrupt cessation
  –Several adverse effects, often dose limiting
• Dantrolene
  –Slow titration
  –Monitor for hepatotoxicity

Fatigue
• Very common symptom in MS
  –Significant burden
  –Often undertreated
• Treatment

–Amantadine (caution renal)
–Methylphenidate

baclofen (Lioreseal)	GABA analogue – binds to GABAB receptors causing: decreased neurotransmitter release and decreased sensory neuron response	periodic LFTs (BL, q6mo) intrathecal (do not abrupt withdrawal) caution renal adj	weakness, sedation, fatigue, dizziness, N, hiccups	- Abrupt cessation may cause seizures and hallucinations - Titrate: 15 mg/day q3d - Doses > 80 mg/day have been used
diazepam (Valium)	Binds to GABAA receptors – enhances endogenous GABA receptor binding leading to increased inhibition	dependence	sedation, cognitive impair, depression	- Abrupt cessation associated with withdrawal syndrome - Sedating - Commonly used as an adjunct to baclofen; rarely used alone
tizanidine (Zanaflex)	Centrally acting α2-agonist – decreases release of excitatory amino acids in spinal interneurons	periodic LFTs (BL, q1,3,6mo) BP (hypo) risk DDI	drowsiness, insomnia, dry mouth, dizziness, hypotension	- Does not alter muscle strength or improve functional measures - Not to be used with anti-hypertensive medications
dantrolene (Dantrium)	Decreases Ca2+ release from skeletal muscle interfering with excitation-contraction of skeletal muscles	periodic LFTs (BL, q3mo) CBC slow titration; monitor hepatotox	hepatotox, weakness, drowsiness, malaise, D	- Due to weakness, most appropriate for patients who are non-ambulatory

Systemic Lupus Erythematosus

https://www.uptodate.com/contents/table-of-contents/rheumatology/lupus

Which is the best drug for the situation?
What are key adverse effects to discuss with the patient?
Is there add-on therapy to consider?

Prevalence: most common in women reproductive age (15-50yo); more severe children, men, those >50yo; most common non-whites

Risk Factors/triggers
- genetic/epigenetic/X chromosome
- hormones
- stress
- viruses/infection
- abnormalities in immune cells and cytokines
- hydrazine, petroleum, solvents, dyes, pesticides, silica dust, cigarette smoke, UV light

Pathophysiology
- predisposing factors - abnormal immune response - autoantibody immune complex - inflammation - end organ damage

Autoantibodies
- nuclear protein - dsDNA - R0/SSA - C1q - La/SSB - Sm - NMDA receptor - phospholipids - blood cells - nucleosomes - histones

Symptoms
- fatigue, depression, anxiety
- photosensitivity
- joint pain (arthritis), HA, nausea/abdominal pain
- weight loss

Signs
- rash, alopecia
- fever
- oral and nasal ulcers
- renal dysfunction
- seizures/psychosis
- pleuritis/pleural effusion, CVD/pericarditis/myocarditis, heart murmur, HTN
- anemia, leukopenia, thrombocytopenia, lymphadenopathy

Cutaneous Lupus Erythematosus

Lupus Nephritis
- Class I/II - Class III/IV - Class V - Class VI

Neurocognitive symptoms
- ischemic stroke/TIA
- seizures
- cognitive dysfunction
- major depression
- neuropathies
- psychosis
- myelitis

Clinical Domain	**Immunological Domain**
Renal: Proteinuria >0.5g/24h Renal biopsy Class II or V Lupus nephritis Renal biopsy Class III or IV Lupus nephritis	Antiphospholipid antibodies: anti-cardiolipin antibodies OR anti-2GP1 antibodies OR Lupus anticoagulant
Hematologic: leukopenia, thrombocytopenia, autoimmune hemolysis	Complement proteins: low C3 OR low C4, Low C3 AND low C4
Neuropsychiatric: delirium, psychosis, seizure	
Mucocutaneous: non-scarring alopecia, oral ulcers, subacute cutaneous OR discoid lupus, acute cutaneous lupus	SLE-specific antibodies: anti-dsDNA antibody* OR anti-Smith antibody
Serosal: Pleural or pericardial effusion cute pericarditis	
Musculoskeletal: joint involvement	
Constitutional: fever	

Goals: improve QoL, prevent flares, decrease disease activity, reduce use of corticosteroids, minimize adverse effects and costs, maintain remission
Comprehensive care: manage comorbidities, exercise, weight control, social support, sun protection, smoking cessation, immunization, counseling
Treatment
FDA approved: aspirin, prednisone, hydroxychloroquine, belimumab (Benlysta)
Off-label: mycophenolate, mofetil, azathioprine, cyclophosphamide, rituximab, leflunomide, abatacept, TNFa inhibitors, IV Ig, OCS, dapson, lenalomide, retinoids

<u>Management of Lupus Nephritis</u>
Adjunctive therapy: - hydroxychloroquine - ACE/ARB
Goals: - BP <130/80 - LDL <100mg/dl
Induction therapy (6 months)
mycophenolate mofetil (preferred black/hispanic): oral 2-3g/d
cyclophosphamide (European whites): IV 500mg q2wk or IV 500-1000mg/m^2 BSA qmo
- glucocorticoids (pulse 3x days) THEN prednisone 0.5-1mg/kg THEN taper to lowest effective dose
Response to Induction
- improved: - MMF 1-2g/d - azathioprine 2mg/kg/d
- not improved: - switch to opposite regimen for six months - rituximab or calcineurin inhibitor (cyclosporine or tacrolimus)

<u>Neuropsychiatric Lupus</u>

no renal dosing: nafcillin, oxacillin, ceftriaxone, clindamycin, azithromycin, erythromycin, moxifloxacin, doxycycline, tigecycline, rifampin

Endocarditis

- Define infective endocarditis (IE) & discuss epidemiology
- Identify patients at risk for IE
- Describe the clinical presentation and diagnosis of IE
- List causative pathogens associated with IE
- Describe empiric and definitive treatment recommendations for infective endocarditis caused by streptococci, staphylococci and enterococci
- Differentiate treatment recommendations for native valve and prosthetic valve infective endocarditis
- Apply guideline recommendations to patient cases

IE definition: infection of endocardial surface of heart (presence of microorganisms); often affects one or more valves (include mural endocardium, septal defects)
Epidemiology: 11 cases/100k; increased hospitalization resulting in mortality up to 20% IE patients; median age 58yo, increases with age; M>F 1.7
Risk factors
- structural heart disease: congenital heart diseases, rheumatic heart disease, degenerative cardiac lesions, mitral valve prolapse
- IVDU; poor definition (tooth); foreign body (prosthetic devices, pacemakers, central venous catheters)

Pathophys: bacterial entry, adherence to damaged endothelium and microthrombi, bacterial proliferation, neutrophil/macrophage infiltration, vegetation form
Complications: CHF, glomerulonephritis, renal/splenic/brain abscess, neurologic damage, mycotic aneurysm, anemia of chronic disease
Clinical presentation
- acute: fulminant course; mortality <6weeks, high fevers, elevated WBC
- subacute: slow, indolent course; mortality >6 weeks; often prior valve disease; low grade fever, night sweats, weight loss; valve systemic: myalgias/fatigue

Pathogens
Acute: *Staph aureus, Strep pneumonia, Strep pyogenes, Neisseria gonorrhoeae
Subacute: Viridans Group Strep (VGS), Strep bovis, CoNS (coagulase-negative staphylococci)
Others: Enterococcus (E. faecalis, E. faecium), HACEK, Pseudomonas, Fungi (Candida, Aspergillus)
Diagnosis:
Signs: heart murmur, Roth's spots (eye), clubbing of extremities, Osler's nodes (finger pain, immunological); embolic phenomena (Janeway lesions, Splinter)
Labs: ↑WBC leukocytosis, anemia (worsens with duration), ↑ESR (erythrocyte sedimentation rate), ↑RF (rheumatoid factor), ↑SCr, positive blood cultures
Imaging: transthoracic echocardiogram (TTE) initial non-invasive, shows right-sided infection; transesophageal echo (TEE) invasive, better visualization

Modified Duke's Criteria

Overall Treatment Principles
Prolonged: high burden of bacteria in vegetations; longer treatment durations, generally 4-6 weeks
Parenteral: maximize PK/PD, higher doses, prolonged/continuous infusions of beta-lactams to max T>MIC; minimal data to support PO tx
Bactericidal: necessary to sterilize vegetations; may require combo or synergstic therapy

Native vs. Prosthetic Valve: major determinant of antimicrobial therapy; prosthetic valves more build up of biofilm
- prosthetic valves often require additional antimicrobials: rifampin, gentamicin

Recommendations by Pathogen
HACEK: Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella
- fastidious gram-negative bacilli, cause 10% of CA-NV-IE in non-IVDU
- bacteremia with these organisms is highly suggestive of IE even without typical physical findings

Duration: for 4wk (NV), 6wk (PV)
*ceftriaxone IV 2g q24h (preferred therapy, another 3rd/4th gen ceph may be substituted)
- ampicillin IV 2g q4h (only if susceptible)
- cipro IV/PO 400mg IV q12h or 500mg PO bid (if unable to tolerate beta-lactam; levo/moxi may be substituted)

Non-HACEK (gram-negative bacilli): very rare; Enterobacteriaceae (E. coli, Klebsiella) or Pseudomonas aeruginosa; Salmonella common outside US
- treatment: cardiac surgery; ID consult recommended
  - combination antibiotic therapy: beta-lactam + (AMG or FQ)

Culture negative IE
- 20% of pt may have negative cultures d/t inadequate microbio techniques, highly fastidious bacteria, nonbacterial pathogens, abx before cultures obtained
- OSUWMC regimen: vancomycin + cefepime/ceftriaxone

NV, acute: S. aereus, β-hemolytic Strep, Gm negative bacilli
NV, subac: S. aureus, Enterococci, VGS, HACEK
PV, <1yr: S. aureus, Enterococci, Gm negative bacilli
PV, >1yr: S. aureus, Enterococci, VGS

Fungal IE
- very rare; risk factors: IDU, immunocomp, cardiovascular device (cath, prosthetic valve, pacemaker)
- most common: Candida spp. and Aspergillus spp.
- valve surgery should be performed in most cases
- antifungal treatment: at least 6 weeks parenteral "induction" therapy: IV amphotericin B +/- PO flucytosine OR echinocandin (Candida spp.)
- after induction lifelong suppressive therapy PO azole

Summary

IE is caused by micro-organism adherence and infection of endocardial surface of heart
Common risk factors include structural heart disease, IDU, foreign materials, and poor dentition
IE can present as an acute or subacute infection
IE can be caused by several infecting organisms, but the most common are Gram positive bacteria, including streptococci, staphylococci and enterococci

Streptococci

Viridans Group Streptococci (VGS)
- S. sanguinis, S. oralis (mitis), S. salivarius, S. mutans; Gemella morbillorum; S. anginosus group (S. intermedius, S. anginosus, S. constellatus) tend to form cardiac abscesses
- normal flora in upper resp tract; leading cause of dental caries; cause of bacteremia, IE, other disorders in immunocomp hosts
- α-hemolytics (partial hemolysis); moderately virulent; gram positive cocci chains = strep

S. gallolyticus (formerly S. bovis): associated with colon cancer
Nutrionally variant streptococci (NVS): - requires vitB12 to grow; Granulicatella app, Abiotrophia defectiva

VGS Treatment
- most strains susceptible to penicillin (PCN) when MIC ≤0.12 mcg/mL; leading cause of dental caries, sign bacteremia, IE, etc in immunocomp
- resistance can occur: 20-30% of VGS cultured after dental procedures were resistant to PCN
  - *never empirically treat with PCN until MIC is known
- cure rates ≥98% with 4 weeks of therapy for PCN susceptible strains
- know treatment differences as MIC rises and becomes more resistant

Penicillin: preferred for patients but continuious infusion, fanny pack
- 12-18M units divided 4-6 doses or CIVI; high dose 24M units when elevated MIC

Ceftriaxone: dosed once a day; no renal adjustment
Gentamicin: 3mg/kg q24h (trough level <1mcg/mL)
Vancomycin: if allergy to β-lactams: 30mg/kg divided in 2 doses (trough goal 10-15mcg/mL)

NVS
- duration 4-6wk; regardless of MIC; rare cause of IE; can treat vancomycin

IV PCN 18-30M units in 4-6 divided doses or CIVI + IV gentamicin 3mg/kg in *2-3 divided doses* 4-6wk

S. pneumoniae, β-hemolytics
Group A (S. pyogenes) Group B (S. agalactiae) Group C F G (S. dysgalactiae subsp. equisimilis, S. canis, S. equi)
- slightly more PCN resistance among groups B C F G compared A
- β-hemolytic strep more virulent, but less common, than α-hemolytics (VGS); usually require cardiac surgery (valve replacement)

Treatment

S. pneumoniae: NVE 4wk; PVE 6wk
- IV PCN 24M units in 4-6 div doses or CIVI or - IV cefazolin 2g q8h or - IV ceftriaxone 2g q24h or - IV vancomycin 30mg/kg in 2 div doses 4-6wk

β-hemolytic strep: NVE or PVE; genta might not be necessary for Group A strep
- IV PCN 24M units or IV ceftriaxone 4-6wk +/- gentamicin 3mg/kg q24h 2wk or - IV vancomycin 30mg/kg in 2 div doses 4-6wk

Streptococci Summary

VGS, S. galloyticus
- MIC <0.12: PCN susceptible
  - NVE
    - IV PCN 4wk
    - IV ceftriaxone 4wk
    - IV PCN or ceftriaxone + IV gentamicin 2wk
      - do not use cardiac abscess, CrCl <20, impaired 8th cranial nerve (auditory/ototoxicity)
  - PVE
    - IV PCN HD +/- gentamicin 6wk
    - IV ceftriaxone +/- gentamicin 6wk
- MIC >0.12 to <0.5: relatively PCN susceptible
  - NVE
    - IV PCN HD 4wk + gentamicin 2wk
    - IV ceftriaxone 4wk (if susceptible)
  - PVE
    - IV PCN + gentamicin 6wk
    - IV ceftriaxone + gentamicin 6wk
- MIC >0.5: PCN resistant
  - NVE
    - IV PCN HD + gentamicin 4-6wk
    - IV ceftriaxone + gentamicin 4-6wk
  - PVE
    - IV PCN + gentamicin 6wk
    - IV ceftriaxone + gentamicin 6wk

Vancomycin: if allergy to β-lactams: 30mg/kg divided in 2 doses (trough goal 10-15mcg/mL)

Staphylococcus species
- normal flora of skin
- differentiate by coagulase
  - positive (e.g. Staphylococcus aureus)
  - negative; CoNS (e.g. S. epidermidis, S. lugdunensis)

Staphylococcus aureus
- *most common cause of IE
- consequence of healthcare contact: intravascular catheters, surgical wounds, indwelling prosthetic devices
- increasing rates of methicillin resistance in hospital and communities: MSSA vs MRSA

Non-IDU: usually left-sided IE, mortality 25-40%, prolonged treatment 6wk

IDU: usually right-sided IE (tricuspid valve); >85% cure rate; in uncomplicated cases can consider 2-4 weeks
  - uncomplicated = no evidence of renal failure, no valves involved, no MRSA
  - IDU inject into veins, contaminated particles go directly to right side of heart via systemic blood flow and damage tricuspid valve

Coagulase-negative Staphylococci (CoNS)
- traditionally associated with prosthetic valves, but native valve IE increasing; similar risk factors overall outcomes as S. aureus; often MRSA
- S. lugdunesis is especially virulent (more like S. aureus)
  - high rate of perivalvular extension and metastatic infection; very susceptible to most abx
- other CoNS: S. epidermidis, S. hominis, S. capitis, S. haemolyticus, S. caprae, S. simulans, many others

MSSA (S. aureus or CoNS) NVE
- IV nafcillin/oxacillin 12g in 4-6 div doses or CIVI for 6wk
- IV cefazolin 6g in 3 div doses for 6wk

If severe anaphylaxis to penicillins?
  - option 1: allergy consult: desensitization procedure
  - option 2: *vancomycin: inferior outcomes and increased mortality compared to β-lactams for MSSA*
  - option 3: daptomycin: no direct studies; non-inferior to standard therapy (antistaph PCN or vanco+genta) for S. aureus bacteremia and IE

MRSA (S. aureus or CoNS) NVE
- IV vancomycin 30mg/kg in 2 div doses (trough goal 10-20) for 6wk
- IV daptomycin ≥8mg/kg q24h for 6 wk if intolerant to vancomycin

MSSA (S. aureus or CoNS) PVE
- IV nafcillin/oxacillin 12g in 4-6 div doses or CIVI ≥6wk + PO rifampin 300mg q8h ≥6wk + IV gentamicin *1mg/kg q8h for 2wk
    - cefazolin may be subbed for naf/ox with non-immediate type hypersensitivity to PCN; vancomycin should be used in patients with β-lactam allergy
    - *notice gentamicin now dosed 1mg/kg q8h for 2 wk; before was 3mg/kg q24h

MRSA (S. aureus or CoNS) PVE
- IV vancomycin 30mg/kg in 2 doses (trough 10-20) ≥2wk + PO rifampin 300mg q8h ≥6wk + IV gentamicin *1mg/kg q8h for 2wk
    - rifampin strong 3A4 inducer (check DDIs); rifampin started after blood cultures are negative
    - *notice gentamicin now dosed 1mg/kg q8h for 2 wk; before was 3mg/kg q24h

Synergy
- gentamicin mostly against gram-negative bacteria; so why using for gram positive strep and staph?
  - β-lactam or vancomycin induces gaps in cell wall (thick peptidoglycan layer)
  - gentamicin now able to penetrate and bind to 30S (also 50S) subunit; inhibits RNA-dependent protein synthesis

Staphylococci Summary

MSSA or MS-CoNS
  NVE
    - IV nafcillin/oxacillin 6wk
    - IV cefazolin 6wk
  PVE
    - IV nafcillin/oxacillin 6wk + rifampin 6wk + gentamicin 1mg/kg q8h 2wk
    - IV cefazolin 6wk + rifampin 6wk + gentamicin 1mg/kg q8h 2wk

MRSA or MR-CoNS
  NVE
    - IV vancomycin 6wk
  PVE
    - IV vancomycin 6wk + rifampin 6wk + gentamicin 1mg/kg q8h 2wk

Enterococci

- normal intestinal flora; may cause serious infections in immunocomp
- E. faecalis and E. faecium (more virulent/more vanco resistant; "umm what do we do next")
  - (97% of enterococcal IE caused by E. faecalis)
- weakly virulent but may be very difficult to eradicate

Enterococcus needs combination therapy

- most abx bacteriostatic against Enterococci
- cell wall-active abx (β-lactams) + AMGs are synergistic and produce bactericidal effect
  - high conc of AMGs necessary; cell wall-active abx ↑permeability of cell which lead to bactericidal effect can be achieved by both abx
- if the Enterococcus strain is resistant to either abx, the combination will not result in bactericidal activity

Enterococci, susceptible to AMG and PCN; NVE or PVE

- IV PCN 18-30M 4-6wk or IV ampicillin 2g q4h 4-6wk + IV gentamicin *1mg/kg q8h 4-6wk
  - 4wk if NVE and sx <3mo; 6wk if NVE sx >3mo; PVE 6wk
- IV ampicillin 2g q4h 6wk + IV ceftriaxone *2g q12h 6wk
  - rec'd for CrCl <50ml/min; notice q12 dosing for ceftriaxone (only other indication used in meningitis)

Enterococci, resistant to AMG, susceptible to PCN; NVE or PVE

- IV ampicillin 2g q4h 6wk + IV ceftriaxone *2g q12h 6wk
- IV PCN/ampicillin + IV streptomycin 15mg/kg in 2 div doses (rarely used)

Enterococci, resistant to AMG and PCN, or PCN allergy; NVE or PVE

- IV vancomycin + IV gentamicin 1mg/kg q8h 6wk
- IV/PO linezolid 600mg q12h 6wk; may cause bone marrow suppression, neuropathy, intx SSRI/MAOI
- IV daptomycin 10-12mg/kg q24h 6wk; monitor CK, may consider amp/ceftaroline in persistent bacteremia or if dapto MIC near breakpoint

Enterococci Summary

PCN + AMG susceptible

- IV ampicillin/penicillin + IV gentamicin 4-6wk (4wk NVE sx<3mo; 6wk NVE sx>3mo; PVE 6wk)
- IV ampicillin + IV ceftriaxone HD 6wk

PCN susceptible, AMG resistant

- IV ampicillin + IV ceftriaxone HD 6wk

PCN resistant or allergy

- IV vancomycin + IV gentamicin 6wk
- IV daptomycin HD 6wk

Indications for surgery
- vegetation size >10mm; persistent bacteremia despite abx; >2 embolic events in first week of abx; gram-negative, fungal; acute CHF, echo

Role of RPh

Drug Considerations/Adverse Reactions
- beta-lactams: usually well tolerated; often require renal adjustment; nafcillin: nephrotox, hepatotox, hypokalemia
- gentamicin: nephrotoxicity, ototoxicity
- rifampin: DDI potent inducer; orange colored body fluids
- vancomycin: nephrotoxicity, Red Man Syndrome (infusion-related)

Dosing/Monitoring
- ceftriaxone
  - streptococci, HACEK: 2g q24h
  - enterococci for synergy: 2g q12h
- vancomycin
  - staphylococci: trough goal 10-20 mcg/ml
  - streptococci: trough goal 10-15 mcg/ml
- gentamicin
  - streptococci (except NVS): 3mg/kg q24h
  - S. aureus, enterococci, NVS: 1mg/kg q8h
  - peak goal 3-5 mcg/ml
  - trough goal <1 mcg/ml

POET trial: IV vs PO, gram-positive (Strep not MRSA, no IDU) left-side endocarditis in stable condition: non-inferior

On exam you should be able to:
▪ Identify risk factors for IE
▪ Identify the most common organisms associated with IE
▪ Choose appropriate therapy based on organism involved
▪ Choose appropriate therapy based on allergies
▪ Choose appropriate therapy based on valve type (native vs. prosthetic)
▪ Choose appropriate therapy based on dose for situations where higher doses are necessary
▪ Choose appropriate duration of therapy based on organism involved and patient factors
▪ Identify key roles for a pharmacist in management of IE, including identification of adverse reactions for antibiotics

Meningitis

- Understand the epidemiology and etiology of meningitis
- Understand the pathophysiology of meningitis
- Recognize the clinical presentation and distinguish its diagnosis by the source of infection
- Recommend empiric and targeted therapeutic treatment plans
- Recommend appropriate preventative strategies

ISDA guidelines: https://academic.oup.com/cid/article/39/9/1267/402080

Meningitis: inflammation of the meninges, three layers of membranes covering the brain and spinal cord
- Dura mater: tough outer layer
- Arachnoid mater: web-like middle layer filled with fluid
- Pia mater: delicate inner layer

Blood Brain Barrier (BBB)
- Composed of tight junctions lining brain capillaries
- Has selective permeability: ↓ penetration = ↑MW, ↑ppb, large hydrophilic molecules, ionized molecules
- Allows small lipophilic molecules, gases, and small polar molecules to diffuse
- Has glucose and peptide transporters
- Meningeal inflammation → increased capillary permeability and impairment of active transporters
- As healing progresses, access of non-lipophilic antibiotics to CSF decreases

Pathophysiology

Sources of infection: contigious spread, hematogenous, direct inoculation, reactivation of latent disease
CNS response: cytokine release (proinflam TNFα, IL-1, platelet activating factor), clotting cascade and (micro)thrombi, vasodilation/permeability, compromised BBB
Cerebral edema: ↑intracranial pressure, ↓cerebral blood flow, ischemia and direct tissue damage

Signs/Symptoms

- headache*, fever*, nuchal rigidty* (inability to bend neck forward to chest), altered mental status*, photophobia, seizures, abnormal CNS findings
  - sensitivity: likelihood true positive result means pt has disease
  - specficitity: likelihood that true negative result means pt does not have disease
  - positive screening: test positive truly has disease
  - negative screening: test negative truly does not have disease
  - presence of two more of the signs* only reach a sensitivity of 45%; absence of two or more of these signs* have negative predictive value of 95%
    - therefore be aware of predictive nature of absence of signs and presence of signs not necessarily being diagnostic for meningitis

Glasgow Coma Scale: eye opening response, verbal response, motor response
  - GCS of 13-15 mild 9-12 moderate ≤8 severe
  - there's also one that has four score domain where pt doesn't have to be awake (no verbal); could be better diagnostic, per review article

Rashes: puperic, petichae: not blanching (press and doesn't fade away); caused by Neisseria meningitis infection
Special pop: - infants: irritability, inactivity, poor feeding, vomiting - elderly: symptoms absent, more subtle

Signs of meningeal irritation	**Maneuver**	**Positive test**
Brudzinski sign - good rule out test	Place patient in the supine position and passively flex the head toward the chest. - low sensitivity, high specificity	The test is positive when there is flexion of the knees and hips of the patient.
Kernig sign - good rule out test	Place patient supine with hip flexed at 90 degrees. Attempt to extend the leg at the knee. - low sensitivity, high specificity	The test is positive when there is resistance to extension at the knee to >135 degrees or pain in the lower back or posterior thigh.
Jolt accentuation of headache	Patient rotates head horizontally two to three times per second.	The test is positive if the patient reports exacerbation of his/her headache with this maneuver.

Risk factors

- social or age factors: infants, teens, young adults, elderly; military/dormitories; travel to sub-Saharan Africa
- CNS structural abnormalities: congenital or presence of CSF shunts, neurosurgery, head trauma
- concurrent disease/immunosupp: URTI, sinusitits, otitis media; alcoholism, HIV, malignancy, asplenia, SOT, smoking

Lab Tests

- CBC with differential + BMP
- blood culture
- lumbar puncture (LP, 'spinal tap')
  - CT prior to LP if immunocomp, hx CNS disease (stroke), new onset seizures, papilloedema, etc
    - main purpose is to exclude possibility of mass lesion which could lelad to cerebral herniation following lumbar puncture
  - LP into subarachnoid space; used to collect CSF (CSF appearance affected by presence of WBC, RBC, bacteria); fluid is gram-stained and cultured

CSF analysis: bacterial: cloudy, 2:3 BG, ↑protein, ↑WBC, 90% neutrophils

	Normal	**Bacterial**	**Viral**
CSF appearance	clear	cloudy	clear-cloudy
Glucose (CSF:Blood)	40-80 (3:2)	<40 (2:3)	≤40
Protein	<50	>150	50-100
WBC count	<5	1,000-5,000	100-500
Differential	>90% mononuclear cells	80-95% neutrophils	>50% lymphocytes

Gram Stain Pathogens

gram(+) cocci *S. pneumoniae (community); S. aureus, CoNS (healthcare)
gram(+) baccili *Listeria monocytogenes
gram(-) cocci *N. meningitidis
gram(-) bacilli Enterobacteriaceae (Kleb, E. coli) (community); P. aeruginosa, Acinetobacter (healthcare)
gram(-) cocbaci H. influenzae

Pathogens
<1month S. agalactiae, L. monocytogenes, E. coli, Klebsiella spp.
1mo-2yo S. pneumoniae, N. meningitidis, H. influenzae, S. agalactiae, E. coli
2-50yo S. pneumoniae, N. meningitidis
>50yo S. pneumoniae, N. meningitidis, L. monocytogenes and aerobic gram(-) bacilli
Head trauma, CSF shunt, neurosurgery: Gram(-) bacilli (including P. aeruginosa), Staphylococcus spp., Streptococcus spp., H. influenzae

Goals of Treatment
Eradication of causative pathogen, Resolve signs and symptoms, Prevent sequelae (hearing loss, focal, cog impair, epilepsy, loss of limb)
Approach: BE AGGRESSIVE; IV high-dose bactericidal agents, those that readily penetrate CNS/BBB; prompt initiation empirically and narrow by culture

Empiric Therapy
<1month ampicillin + AMG/cefotaxime
1mo-2yo vancomycin + cefotaxime/ceftriaxone*
2-50yo vancomycin + cefotaxime/ceftriaxone
>50yo vancomycin + ampicillin + cefotaxime/ceftriaxone
Head trauma, CSF shunt, neurosurgery: vancomycin + cefepime/ceftazidime/meropenem (to cover for Pseudomonas)

Targeted Therapy

N. meningitidis	7 days	3rd-gen cephalosporin (if MIC 0.1-1 mcg/ml); if MIC <0.1 ampicillin/penicillin G can be used
H. influenzae	7 days	3rd-gen cephalosporin
S. pneumoniae	10-14 days	vancomycin + 3rd-gen cephalosporin
S. agalactiae	14-21 days	ampicillin/penicillin G
E. coli & Klebsiella	21 days	3rd-gen cephalosporin
P. aeruginosa	21 days	ceftazidime/cefepime/meropenem
L. monocytogenes	≥21 days	ampicillin/penicillin G

Adjunct Therapy
Corticosteroids (dexamethasone): inhibits release of pro-inflammatory cytokines, limits CNS inflammatory response, theoretically reduces neurologic damage
- Indications: • Adults with suspected or proven pneumococcal meningitis • Infants and children with H. influenzae type B meningitis • Not for neonates
Time of initiation: First dose 10-20 minutes before initial antibiotic and no later than first antibiotic dose; NOT recommended if patient has received antibiotics
Dose and duration: Give 0.15 mg/kg IV q6h for 2-4 days (adults/children)
Caution: reduces vancomycin penetration to CSF by 42-77%

Efficacy of Treatment
• Response to therapy: Clinical signs/symptoms resolve? Did labs improve (CBC, BMP, Vitals)?
• Did complications develop? seizure, hearing loss, focal deficit
• CSF & Blood Cultures typically not repeated if the patient improves

Safety
ampicillin: pencillin allergy; requires renal adjustment
cephalosporins: penicillin allergy; some require renal adjustment; ceftriaxone contraindicated in neonates
AMGs: renal and otoxicity (esp renal impairment or prolonged use); narrow therapeutic index (peak 7-10, trough <1)
vancomycin: requires serum trough monitoring <1; renal dosing; hypersensitivity reactions (allergy vs. Red Man-avoid by doing 1g/hr, itchy responds to AH)
meropenem: renal dosing; DDI decrease serum valproate (less likely to cause seizures compared to imipenem)
C. difficile infection: associated with prolonged abx use; monitor for stool changes

Prevention, Vaccination
S. pneumoniae: >65yo Prevnar13 and Pneumovax23; pediatrics Prevnar13
H. influenzae type B: pediatric combination products
N. meningitidis: common serogroups BCY; many vaccine types (ACWY-Menactra, B-Bexsero)

Prevention, Chemoprophylaxis
• Indicated for those in close contact with an infected patient (family, roomates); off-label
• Initiate as soon as possible after exposure; use after 14 days of suspected exposure is of no benefit
rifampin N. meningitidis: 600mg bid x 4 doses (ped 5-10mg/kg bid x 4 doses) H. influenzae type B: 600mg/day x 4 doses (ped 20mg/kg/d x 4 doses)
cipro N. meningitidis: 600mg PO once
ceftriaxone N. meningitidis: 150mg IM once (<15yo 125mg IM once)

Summary
• Meningitis is a neurologic emergency
• Patients with fever, headache, and nuchal rigidity should be evaluated
• Empiric therapy should be targeted for age and most likely pathogen
• Narrow therapy based on lab data and clinical response

• Monitor for efficacy and safety

Viral Hepatitis

- List differences between the five types of viral hepatitis
- Identify modes of transmission, risk factors and prevention strategies for each type of viral hepatitis
- Discuss the difference between acute and chronic hepatitis
- Provide treatment goals for a patient with chronic viral hepatitis
- Develop a pharmaceutical care plan for the treatment of chronic viral hepatitis
- Formulate a monitoring plan to assess the safety and efficacy of medications used to treat chronic viral hepatitis

https://www.uptodate.com/contents/table-of-contents/infectious-diseases/hepatitis

Viral Hepatitis: inflammation of liver caused by viruses: A B C D E
- viruses most common cause of hepatitis: predominately A B C
- presents as acute and/or chronic illness (based on diseases duration)

		Route	Vaccine	Typical Course	Notes
HAV	RNA	fecal-oral	Yes	Acute	
HBV	DNA	blood/body fluids	Yes	Acute→Chronic	
HCV	RNA	blood/body fluids	No	Chronic usually	
HDV	*	blood/body fluids	No	Acute→Chronic	*incomplete RNA virus; requires HBV for replication
HEV	RNA	fecal-oral	No	Acute	

Acute Viral Hepatitis
- acute defined as infection present less than <6 months
- mostly self-limiting, may persist to chronic; death rare but acute viral hepatitis can result in acute liver failure; LFTs/serologic tests for diagnosis

Clinical Presentation
- incubation period: asymptomatic
- prodromal (pre-icteric) phase: many remain asymptomatic but can have nonspecific flu-like symptoms: anorexia, nausea, fatigue, malaise, fever, RUQ pain
- icteric phase: dark urine, acholic stools, pruritis, icteric sclera, hepatomegaly, mild weight loss
- recovery phase: jaundice fades (2-4wk); liver enzymes return to normal

Pathology: virus infects hepatocyte which presents MHC I → CD8 T-cell recognizes MHC I →cytotoxic killing of hepatocyte → cell apoptosis → liver inflamm, fibrosis, cirrhosis, cancer

Treatment: self-limited disease (supportive treatment); rest, maintain fluid balance; avoid alcohol and hepatotoxic drugs

Hepatitis A Virus (HAV)
ssRNA picornavirus; 1.4M cases/yr world; fecal-oral transmission; correlates low SE status lol
Risk factors: international travelers; homosex; food-waterborne outbreaks

HAV Prevention: adherence to sanitation (hand washing, heating foods, avoid water/food endemic areas)
Vaccines all children >1yo, those likely to be exposed

	Vaccine	Age	Dose	Vol	Schedule			
					1st	2nd	3rd	4th
A	HAVRIX	1-18 yo	720 EL.U	0.5 mL	0 mo	6-12 mo	-	-
		≥19 yo	1440 EL.U	1 mL				
	VAQTA	1-18 yo	25 U	0.5 mL	0 mo	6-18 mo	-	-
		≥19 yo	50 U	1 mL				
A/B	TWINRIX	≥18 yo	720 EL.U/20 ug	1 mL	0 mo	1 mo	6 mo	-
					0 day	7 day	21-30 day	12 mo

Hepatitis D Virus (HDV)
incomplete RNA virus that requires helper function of HBV; blood/body fluid transmission; duration determined by HBV infection;
coinfection: HBV/HDV may occur simultaneously superinfection: acquiring HDV after previous infection with HBV; high risk of severe chronic liver disease
prevention: immunization against HBV; education for those with chronic HBV

Hepatitis E Virus (HEV)
most common cause of acute worldwide (rare in US); fecal-oral transmission (uncooked seafood)
genotypes 1 2: waterborne (fecal contamination) genotypes 3 4 foodborne sporadic cases (undercooked meat; can circulate in animals)
fulminant hepatic failure (<3%): pregnant* (25%), malnourished, preexisting liver disease
prevention: travelers to endemic areas (Asia, Africa, ME, Centra America) should avoid drinking water, uncooked shellfish, fruits/veggies, meats

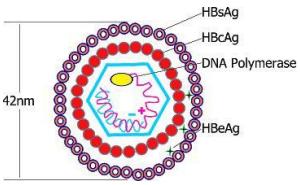
Chronic Viral Hepatitis
- chronic defined as ongoing hepatocellular necrosis for ≥6 months or beyond the onset of acute illness
- causes: B C D
- prevention and treatment may prevent end stage liver disease (ESLD)

Natural History of Chronic Hepatitis Infection (progression over 10 to 50 years)
Acute Hepatitis → Clearance/Resolution (HBV 90-95%; HCV 15-25%)
Chronic Hepatitis (HBV 6-10% >5yo; HCV 75-85%) ←→ Inactive disease (HBV only; inactive replication latency, may reactivate; active replication)
Cirrhosis (HBV 15-25%; HCV 5-20%)
- Decompensation (HBV 2-5%/yr; HCV 3-6%/yr) - HCC (HBV 6-15%; HCV 1-5%)
Death (HBV 15-25%; HCV 1-5%)

Hepatitis B
250M+ living with chronic worldwide; 1.0/100,000 in US; majority unaware they're infected; chronic HBV most often leads to liver failure
Transmission (can survive outside body for 7 days, use bleach)
- #1 IVDU, #2 sexual contact; others: blood-blood, hemodialysis, occupational exposure, infected woman to newborn during delivery

Hepatitis B Diagnosis and Serology

Serology Marker	**Abbrev**	**Signficance**
Hepatitis B surface antigen	HBsAg	indicates infection either acute or chronic
Hepatitis B E (early) antigen	HBeAg	indicates active viral replication
HepB surface antibody*	**HBsAb or Anti-HBs**	**immunity to HBV (passive or active)**
HepB core antibody	HBcAb or Anti-HBc	appears at sx onset and persists for life
HBV PCR		quantifies presence of HBV DNA



	Acute HBV	**Chronic HBV**	**Cleared HBV**	**Vaccinated**	
HBsAg	+	+	-	-	HBsAg positive means antigen present therefore active infection
HBsAb	-	-	+	+	
HBcAb IgG	+	+	+	-	
HBcAb IgM	+	-	-	-	HBcAb IgM presence can differentiate between acute vs. chronic

- body will intitially produce antibodies against core antigen (HBcAb, IgM then IgG) but will need to produce antibodies against surface antigen (HBsAb) to clear the virus
- vaccination skips the steps of making antibodies against core antigen (HBcAb) and goes straight to providing immunity through surface antibodies (HBsAb)

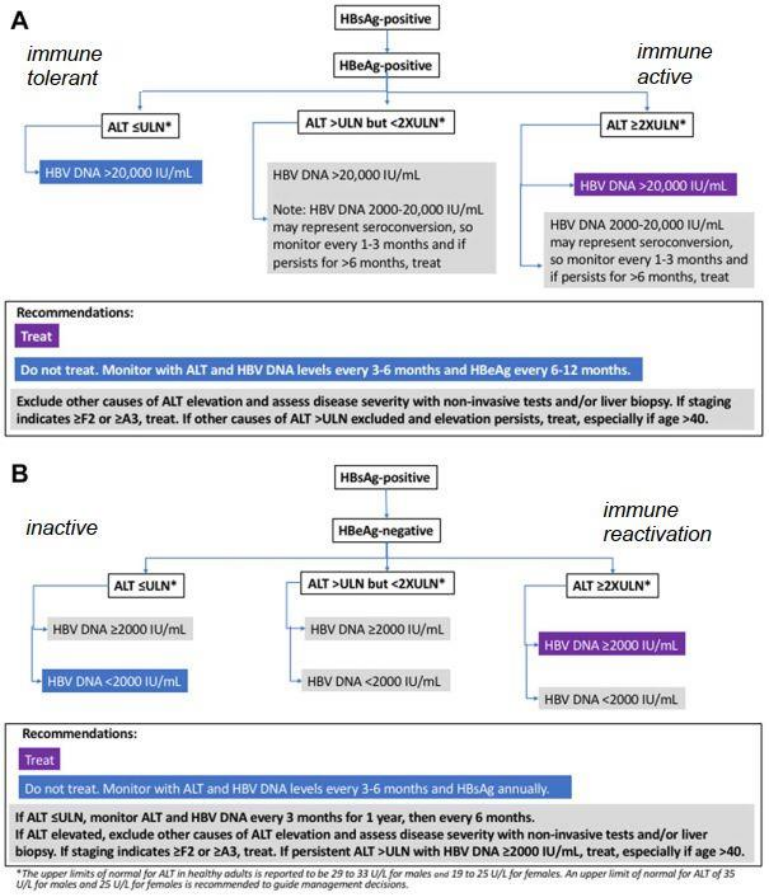
Interpretation of Hepatitis Battery, Chronic
No infection or immunity: HBsAg (-) HBsAb (-) HBcAb IgG/IgM total (-)
Immunity from vaccine: HBsAg (-) HBsAb (+) HBcAb IgG/IgM total (-)
Immunity from exposure: HBsAg (-) HBsAb (+) HBcAb IgG/IgM total (+)
Active infection: HBsAg (+) HBsAb (-) HBcAb IgG/IgM total (+) HBeAg (+) HBVDNA/PCR (high)

*chronic vs. acute look for HbcAb IgM (-) for chronic

https://www.uptodate.com/contents/hepatitis-b-virus-overview-of-management

Phases of Chronic Hepatitis B Infection

	Viral repl HBeAg	HBV DNA IU/mL	ALT level	Liver Damage
Phase 1 (immune tolerant)	+	high >1M	normal	none/minimal
Phase 2 (immune active)	+	≥20,000	↑	moderate/severe
Phase 3 (inactive carrier)	-	<2,000	normal	none
Phase 4 (immune reactivation)	-	≥2,000	↑	moderate/severe



Treatment of Chronic HBV

Goals of Chronic HBV Treatment:
- sustained suppression of viral replication - prevent liver failure/cancer

Who/When
A immune active
B immune reactivation

What
Interferon-α; Peg-INF-alpha-2a (Pegasys): preferred in HBV-HDV superinfection
Nucleos(t)ide Analogs (NAs)
- entecavir (ETV) (Baraclude)
- tenofovir alafenamide (TAF) (Vemlidy)
- tenofovir disoproxil fumarate (TDF) (Viread)
- Others: adefovir (ADV), lamivudine (LAM), telbivudine (TDV)

Duration: 12 months; indefinite

tenofovir

MoA: NtRTI A, inhibits RT of RNA to HBV DNA

TDF: 300mg qd; metabolism plasma; excess exceted kidneys; renal adj CrCl <50
- preferred pregnancy; worse eGFR, worse BMD

TAF: 25mg qd; metabolism intracellularly; rapid absorption; no renal adjustment

SE: HA, N, fatigue

Warning: BBW lactic acidosis; DF: nephrotox, Fanconi syndrome, osteomalacia

Resistance: 0% at 1 and 5 years; adefovir cross-resistant; preferred in LAM-resistant

Monitor: renal function, lactic acid, HIV prior testing; TDF monitor BMD

entecavir

MoA: NRTI G

Dosing: 0.5mg qd (nucleoside-naïve adults); 1mg qd (LAM/TDV-experienced or decompensated cirrhosis)
- adjust CrCl <50

SE: HA, N, fatigue

Warning: BBW lactic acidosis; hepatomegaly

Resistance 0% at 1yr, 1.2% at 5yrs; higher in pt with hx LAM-resistance (51% at 5yrs)

Older Chronic HBV Therapies

Peg-INF-alpha-2a Pros: finite tx period (48wk), weekly dosing, minimal resistance, more durable response
Cons: Side effects (mood disturbances, fatigue, flu-like sx); several contraindications

lamivudine (LAM) Pros: well-tolerated (mild fatigue, NVD, HA, rash, anemia)
Cons: high resistance (27% at 1yr, 65% at 5yrs); LAM resistance increases ETV resistance but not tenofovir resistance; risk of nephrotoxicity

adefovir (ADV) Pros: effective for tx with LAM-resistance
Cons: resistance (0% at 1yr, 42% at 5yrs); ADV resistance decreases susceptibility to tenofovir

telbivudine (TDV) Pros: slightly more potent effects than LAM/ADV
Cons: resistance (4.4% at 1yr, 21% at 5yrs); TDV resistance increases ETV resistance but not tenofovir resistance; not effective in LAM-resistance

Duration (not well established)

- should stop if confirmed HBsAg negative
- can stop in HBeAg positive pt without cirrhosis who 1. achieve HBeAg seroconversion (HBeAg negative), 2. have undetectable HBV DNA, and 3. have completed >12mo treatment
- treatment may be indefinite if seroconversion does not occur
- drug resistance is a serious risk of prolonged NA therapy
- liver transplant may be required

Response to Treatment

*slide 45

Prevention (HD/IC = hemodialysis and other immunocompromised patients)

Vaccine	Age	Dose	Vol	Schedule			
				1st	2nd	3rd	4th
Heplisav-B	>18 yo +/- HD/IC	20 µg	0.5 mL	0 mo	1 mo	-	-
Recombivax HB	0-19 yo +/- HD/IC	5 µg	0.5 mL	0 mo	1 mo	6 mo	-
	≥20 yo	10 µg	1.0 mL				
	≥20 yo + HD/IC	40 µg	1.0 mL				
Engerix-B	0-19 yo +/- HD/IC	10 µg	0.5 mL	0 mo	1 mo	6 mo	-
	≥20 yo	20 µg	1.0 mL				
	≥20 yo + HD/IC	40 µg	2.0 mL	0 mo	1 mo	2 mo	6 mo

HBV Vaccine candidates:
- all infants, beginning at birth
- high risk adults not previously vaccinated
  - homosex, IVDU (current/recent), ESRD/dialysis, diabetes, recipients of clotting factors, healthcare providers, international travelers, chronic liver disease, HIV infected, incarcerated

Hepatitis C
ssRNA virus; 180M worldwide (4-5M US); half are unaware; very common blood-borne infection; CDC screen high risk ppl and born 1945-65; USPSTF screen all 18-79yo
HCV genotypes: at least 7 distinct HCV genotypes (1-6) and subtypes
- genotype 1 most prevalent in US; genotype 4,5,6 in Egypt south Africa Asia, respectively
- viral genotyping may determine differences in treatment option/duration

Transmission: IVDU, tattoos/piercing, sex, mother-to-infant, occupational, organ/tissue transplant, nosocomial/hospital
Diagnosis
- ELISA screening tests (OraQuick HCV rapid antibody test); watch for false negatives
- HCV antibody: positive test indicates exposure (not active infection); detectable 8-12 weeks post exposure
- HCV RNA **PCR**: presence of HCV RNA indicates **active infection**; used in monitoring response to treatment

Initial (Pretreatment) Assessment
- confirm/rule out cirrhosis: - FIB-4 score (age, AST, ALT, platelets) - serum biomarkers (FibroSure)
- liver transient elastography >12 cirrhotics (FibroScan)
- liver biopsy, histology: fibrosis (stage), inflammation (grade)
- pretreatment labs: - anytime prior: HCV RNA by PCR, HIV test, HBsAg - within 6 months: CBC, hepatic function panel, chemistry panel - immediately prior: pregnancy
- medrec and DDI assessment

HCV Counseling
- avoid transmission: avoid shaving/dental equipment, cover wounds, stop IV/INDU, no donation, low risk for sex partners, clean bloody surfaces with bleach
- avoid disease progression: abstinence from illicit drugs and alcohol; abstinence from hepatotoxic medications (APAP max 2g/day)

Goals of Chronic HCV treatment:
- eradicate infection - Sustained Virologic Response (SVR) - improve fibrosis/reduce progression

Evolution of Treatment:
then: combination PEG-IFN + ribavirin (RBV) was standard; both SC, duration 24-48wk; lots of SE (flu-like, depression, bone marrow supp, alopecia, fatigue)
now: duration as little as 8 weeks, all oral, minimal SE

Epclusa: VEL/SOF
velpatasvir 100mg/sofosbuvir 400mg — 1 tablet once daily
SE: HA N fatigue; mild hard to see if SE from drug or of virus; SE profile worse with worse disease
Use: pan-genotypic; preferred in decompensated cirrhosis
Intx: VEL/SOF (P-gp substrate)
↓VEL/SOF effect if given with anticonvulsants (carbamazepine, phenytoin), rifampin, St. John's wart
↑VEL/SOF effect if given with clarithromycin, antifungals
VEL/SOF effect on other drugs: ↑statins, digoxin
Effect on VEL (pH sensitiv): antacids (separate 4hrs); H2RAs (sametime or separate 12hrs; max famotidine 40mg bid); PPIs not rec'd, if nec VEL/SOF w food 4h prior (max omep 20mg)

Vosevi: VEL/SOF/VOX
velpatasvir 100mg/sofosubuvir 400mg/voxilaprevir 100mg — 1 tablet once daily with food
SE: HA N fatigue
Use: failed newer DAAs or treatment-resistance in GT3
Intx: VEL/SOF/VOX (P-gp substrate)
↓VEL/SOF/VOX effect if given with anticonvulsants (carbamazepine, phenytoin), rifampin, St. John's wart
↑VEL/SOF/VOX if given with antifungals
VEL/SOF/VOX effect on other drugs: ↑statins, digoxin
Effect on VEL (pH sensitiv): antacids (separate 4hrs); H2RAs (sametime or separate 12hrs; max famotidine 40mg bid); PPIs not rec'd, if nec VEL/SOF w food 4h prior (max omep 20mg)

Mavyret: GLE/PIB
glecaprevir 100mg/pibrentasvir 40mg — 3 tablets once daily with food
SE: HA N fatigue
Use: pan-genotypic; shorter durating in treatment-naïve patients (8 wk); never use decomp cirrhotic patient
Intx: GLE/PIB (3A4 metabolite)
↓GLE/PIB effect: anticonvulsants (carbamazepine, phenytoin), rifampin, St. John's wart
↑GLE/PIB effect: antifungals
GLE/PIB effect on other drugs: ↑statins, dabigatran, ARBs
Package insert does not say avoid PPIs but omep 40mg 1hr before shown to decrease drug conc by 64%; rec'd to avoid doses >20mg
Avoid use: ethinyl estradiol (including patch/ring)

ribavirin
≤75kg: 1000mg/d in two divided doses; >75kg: 1200mg/d in two divided doses; "low dose ribavirin": start with initial 600mg daily (increase as tolerated)
SE: NV fatigue, hair thinning, rash/dry skin, cough, anemia
Intx: do not coadminister didanosine; concomitant use of ribavirin and azathioprine accumulation of azathioprine metabolite and subsequent myelotoxicity
CI: pregnant women and men (whose partner is pregnant); CrCl <50; hemoglobinopathies; known hypersensitivity SJS, toxic epidermal necrolysis (TEN), erythema multiforme
- Pregnancy Cat X (male and female): must use two forms of contraception during treatment and at least 6mo after

- must have negative pregnancy test before starting therapy

Treatment

https://www.uptodate.com/contents/overview-of-the-management-of-chronic-hepatitis-c-virus-infection https://www.hcvguidelines.org/

Have the received treatment before? Are they cirrhotic, compensated cirrhotic, or decompensated?

	Compensated Cirrhosis		**Decompensated Cirrhosis**	
Stage	Stage 1	Stage 2	Stage 3	Stage 4
Clinical	no varices no ascites	varices no ascites	ascites +/- varices	bleeding +/- ascites
Death (at 1yr)	1%	3%	20%	57%

Treatment of Chronic HCV: Simplified

Naïve HCV

Non-Cirrhotic

- glecaprevir/pibrentasvir (Mavyret) x 8 wk
- velpatasvir/sofosbuvir (Epclusa) x 12 wk

Cirrhotic: Compensated

- glecaprevir/pibrentasvir (Mavyret) x 8 wk
- velpatasvir/sofosbuvir (Epclusa) x 12 wk (only genotype 3 patients who've ruled out Y93H resistance test)

Cirrhotic: Decompensated

- ledipasvir/sofosbuvir (Harvoni); typically add ribavirin or extend treatment duration to 24 weeks if unable to tolerate ribavirin
- velpatasvir/sofosbuvir (Epclusa); typically add ribavirin or extend treatment duration to 24 weeks if unable to tolerate ribavirin

Experienced HCV: Peg-INF/ribavirin-experienced

Non-Cirrhotic; G12456

- glecaprevir/pibrentasvir x 8 wk
- velpatasvir/sofosbuvir x 12 wk

Non-Cirrhotic, G3

- glecaprevir/pibrentasvir x **16 wk**
- velpatasvir/sofosbuvir x 12 wk (r/o Y93H resistance)
- velpatasvir/sofosbuvir/voxilaprevir x 12 wk (if Y93H resistance marker present)

Compensated Cirrhotic, G12456

- glecaprevir/pibrentasvir x **12 wk**
- velpatasvir/sofosbuvir x 12 wk

Compensated Cirrhotic, G3

- glecaprevir/pibrentasvir x **16 wk**
- velpatasvir/sofosbuvir/voxilaprevir x 12 wk

Experienced newer DAA:

- refer to guidelines; based on previous exposure(s); treatment options who have failed newer DAAs are limited
- in general can use (with some exceptions):
  - glecaprevir/pibrentasvir (Mavyret)
  - velpatasvir/sofosbuvir/voxilaprevir (Vosevi)

General Monitoring

**Sustained Virologic Response (SVR12) is when HCV RNA is undetectable 12 or more weeks after completion of treatment

Special Populations

HIV coinfection: treatment same but consider DDIs

Decompensated cirrhosis: ledipasvir/sofosbuvir and velpatasvir/sofosbuvir preferred; typically add ribavirin or extend treatment duration to 24 weeks if unable to tolerate ribavirin

Posttransplant: refer to guidelines, consider DDIs

Pregnancy: treat prior or after, not during

RPH Role in Chronic HCV: assist with guideline appropriate therapy, determine formulary preferred option; screening for DDIs, patient counseling, f/u monitor to ensure cure

Summary

- Viral hepatitis is the leading cause of hepatitis worldwide
- Five types currently identified
- Routes of transmission differ among types – PREVENTION is KEY
- Can lead to acute or chronic hepatitis
- Treatment of chronic HCV rapidly developing field requiring pharmacist involvement
- Appropriate treatment and monitoring necessary to prevent progression and complications of ESLD

HIV

HIV Screening

Symptoms of Acute Infection: when in doubt draw HIV RNA viral load

HIV =\= AIDS
HIV is retrovirus which must convert RNA to DNA to build HIV proteins; RTase generates cDNA from RNA template

Lab Values
- CD4 count correlates to overall immune function; monitored q3-6mo following dx; if CD4>300 can do q1y
- HIV-1 RNA viral load is a marker for response to ART
  - monitored q2-8wk after ART initiation/modification; q4-8wk until undetectable; once UD, q3-6mo
  - HIV-2 RNA viral load not avail in US due to rarity (frequent in Africa)

Resistance
- wild-type virus considered most virulent/infectious/fastest replicating
- HIV can mutate back and forth from wild-type based on external stimuli (drugs) and time; have to include all prev point mutations in database search

Goals of Therapy
- to obtain undetectable viral load; goal <200 copies/ml (can detect down to 20 copies/ml)
- to increase or prevent decline in CD4; goal >200 cells/mm3 for decreased risk of OIs; (normal CD4 500-1200)
- reduce HIV related morbidity and prolong duration/quality of life
- prevent HIV transmission

ART Therapy
- for everyone regardless of CD4 count; treatment as prevention (U=U)
  - ART reduces VL, other morbidities of HIV (due to reduction of chronic low-level inflammation): HIV-ass neurocog disorder, HIV-nephropathy, HIV-neuropathy, ASCVD risk
- ART deferral or “drug holidays” rarely considered (for inadherence or elite controllers (low VL, CD4 high) or chronic nonprogressors (very high VL, CD4 unaffected))
- rapid initiation upon diagnosis (POC ab/ag test); start within 14 days of dx
- retained in to care, on medicine, and undetectable = decreases in new infections
- HIV care continuum: dx, linked to care, received HIV care, retained in care, achieved viral suppression

NRTIs (Nucleoside and Nucleotide Reverse Transcriptase Inhibitors)	
abacavir (ABC)	Ziagen
didanosine (ddI)	Videx
emtricitabine (FTC)	Emtriva
lamivudine (3TC)	Epivir
stavudine (d4T)	Zerit
tenofovir af (TAF)	Vemlidy
tenofovir df (TDF)	Viread
zidovudine (ZDV, AZT)	Retrovir

NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors)	
doravirine (DOR)	Pifeltro
efavirenz (EFV)	Sustiva
etravirine (ETR)	Intelence
nevirapine (NVP)	Viramune
rilpivirine (RPV)	Edurant

INSTIs (Integrase Strand Transfer Inhibitors)	
dolutegravir (DTG)	Tivicay
elvitegravir (EVG)	Vitekta
raltegravir (RAL)	Isentress
bictegravir (BIC)	in Biktarvy

PIs (Protease Inhibitors)	
ritonavir (RTV) PK boosting	Norvir
saquinavir (SQV)	Invirase
indinavir (IDV)	Crixivan
fosamprenavir (FPV)	Lexiva
atazanavir (ATV)	Reyataz
darunavir (DRV)	Prezista
nelfinavir (NFV) non-peptidomimetic	Viracept
tipranavir (TPV) non-peptidomimetic	Aptivus

Misc (Entry Inhibitors)	
Fusion inhibitor enfuvirtide (T-20)	Fuzeon
CCR5 antagonist maraviroc (MVC)	Selzentry
Attachment inhibitor fostemsavir	Rukobia
Post-attachment inhibitor ibalizumab	Trogarzo

PK enhancers	
ritonavir (RTV/r)	Norvir
cobicistat (c)	Tybost

Fixed-dose combinations		
abacavir-lamivudine	Epzicom	(ABC/3TC)
abacavir-lamivudine-zidovudine	Trizivir	(ABC/3TC/ZDV)
bictegravir-emtricitabine-tenofovir af	Biktarvy	(BIC/FTC/TAF)
darunavir-cobicistat-emtricitabine-tenofovir af	Symtuza	(DRV/COBI/FTC/TAF)
dolutegravir-abacavir-lamivudine	Triumeq	(DTG/ABC/3TC)
dolutegravir-lamivudine	Dovato	(DTG/3TC)
dolutegravir-rilpivirine	Juluca	(DTG/RPV)
doravirine-lamivudine-tenofovir df	Delstrigo	(DOR/3TC/TDF)
efavirenz-emtricitabine-tenofovir df	Atripla	(EFV/FTC/TDF)
elvitegravir-cobicistat-emtricitabine-tenofovir af	Genvoya	(ECF/TAF or EVG/COBI/FTC/TAF)
elvitegravir-cobicistat-emtricitabine-tenofovir df	Stribild	(ECF/TDF or EVG/COBI/FTC/TDF)
rilpivirine-emtricitabine-tenofovir af	Odefsey	(RPV/FTC/TAF)
rilpivirine-emtricitabine-tenofovir df	Complera	(RPV/FTC/TDF)
tenofovir af-emtricitabine	Descovy	(TAF/FTC)
tenofovir df-emtricitabine	Truvada	(TDF/FTC)
zidovudine-lamivudine	Combivir	(ZDV/3TC)
lopinavir/ritonavir (PI combination)	Kaletra	(LPV/r)
darunavir-cobicistat (PI combination)	Prezcobix	(DRV/COBI)
atazanavir-cobicistat (PI combination)	Evotaz	(ATV/COBI)

<u>NRTIs</u>
- backbone of HIV therapy consists of 2 nukes
- competitive substrate inhibitors: mimicks deoxynucleotides, compete for incorp into DNA chain, lack 3'OH chain termination
- commonly co-formulated
- typicall well-tolerated
  - SE: HA ND dizziness resolve within 1-2 weeks
  - other SE not really seen in newer therapies: lipoatrophy (wasting), hepatic steatosis, lactic acidosis, anemia
- DDI: not many; ethanol may increase abacavir
  - TDF and other nephrotoxic agents (watch NSAIDs, cyclosporine, AMGs, amphoB)
  - 3A4 inducers ↓TAF (contraindicated): rifampin, carbamazepine, oxcarbazepine, St. John's Wort

zidovudine: can cause anemia; failed single agent due to resistance (increased doses = lactic acidosis); 300mg bid adult; given IV at birth to mothers with VL>1000 copies/ml
didanosine: 400mg qd; SE: pancreatitis, parathesias/neuropathies; no longer rec'd
tenofovir: TDF 300mg qd, TAF 25mg qd (or 10mg qd when used with cobicistat); ↓renal function and ↓bone density (TAF less drug/less exposure); well tolerated
abacavir: 600mg qd; associated ↑MI
  - MUST due HLA-B*5701 testing prior to initiation: if (+) do not use, increased hypersensitivity rxn; rxns can occur if HLA (-) fever, rash* (life-threatening), NVD, fatigue/achiness, SOB
lamivudine: 300mg qd, Cytidine analog, co-form with abacavir; M184V wipes out activity, however boosts activity of TDF/TAF, AZT, d4T
emtricitabine: 200mg qd, Cytidine analog, co-form with tenofovir; M184V wipes out activity, however boosts activity of TDF/TAF, AZT, d4T
stavudine: not used
zalcitabine: not used

HBV/HIV coinfection: TDF/TAF + FTC + 3rd agent (NNRTI/PI/INSTI)
  - tenofovir, lamivudine, emtricitabine all have HBV activity; however due to HBV resistance rates, coinfection HBV/HIV, use combo of TDF/TAF + FTC + 3rd agent (NNRTI/PI/INSTI)

<u>NNRTIs</u>
- non-nukes, have lowest genetic barrier to resistance
- binds directly to RT, inhibits movement of protein domains that are needed for DNA synthesis
- HIV-1 only, *not* HIV-2
- tend to be lipophilic, cross BBB, CNS side effects: dizziness, drowsy, CNS depression, fogginess; can cause rash, hepatotoxicity as lipophilic drugs tend to be hepatically metabolized
- DDIs:
  - efavirenz, nevirapine, etravirine 3A4 inducers
  - efavirenz ↓AUC of methadone by 52% (withdrawal) - EFV, NVP, ETR ↓most statins (rosuvastatin, pitavastatin excluded)
  - ↓estradiol derivatives (contraception, gender hormones)
  - rifabutin/rifampin and St. John's Wort ↓ most and all NNRTIs, respectively

nevirapine: 200mg IR qd x14d, if no rash, 400mg ER qd; dosing to watch for SJS; life-threatening hepatotoxicity, use only benefit>risk; K103N mutation wipes out activity
efavirenz: 400-600mg qHS* d/t SE dizziness/drowsiness, vivid dreams common; take on empty stomach (fatty meal inc absorption/toxicity); K103N mutation wipes out activity
etravirine: 200mg bid after meal; higher barrier to resistance compared to other 1st-gen NNRTIs; completely kidney safe (option for dialysis patients)
rilpivirine: 25mg qd with meal ≥400 calories* with some being from fat; must be absorbed in acidic environment (PPIs contraindicated); not used when VL >100,000 or CD4 <200

doravirine: 100mg qd; 2nd-gen; higher barrier for resistance; well tolerated
delavirdine: not used

PIs
- HIV protease cuts long chain proteins (polypeptides) that include RT, Integrase, Protease
- highest genetic barrier to resistance as a class; most PIs require multiple point mutations before activity wiped out
- require PK enhancing/boosting by either ritonavir or cobicistat
- CYP inhibition, lots of DDIs; since hepatically metabolized, can be used frequently in renal insufficiency
- SE: GI NVD, diarrhea* common; metabolic effects: lipodystrophy, hyperglycemia, hyperlipidemia; ↑LFTs; nephrolithiasis (kidney stones) uncommon but with indinavir and atazanavir
- DDI: avoid simva/lova; reduce atorva/rosuva <20mg
  - inhaled CS accum can lead to Cushing's syndrome (beclomethasone safest)
  - amphetamines watch doses
  - antiepileptics (carb, oxcarb, phenytoin)
  - contraceptives ↓serum estrogen failed birth control
  - avoid coadmin with CYP inducers (rifampin, carb, oxcarb, SJW)

darunavir: 800mg + 100r or 150c qd (600+100r bid less common); best tolerated PI (least SE incidence); only PI in STR
atazanavir: 300mg + 100r or 150c qd (400mg qd); only PI that can be given unboosted (400mg qd), must be boosted when given with TDF; benign hyperbilirubinemia* (jaundice/scleral icterus); must be acidic environment (PPIs contraindicated)
fosamprenavir: barely used anymore; 500mg + 100r bid (1400mg + 200r qd)
lopinavir: 800mg + 200r qd (400mg +100r bid); lots of pregnancy data however no longer used due to comparative tolerability of DRV
ritonavir: 100mg with each dose of PI; not used for treatment d/t tolerability and rapid metabolism; used as boosting agent due to high 3A4 inhibtion/affinity
indinavir, nelfinavir, saquinavir, tipranavir: not used

INSTIs
- after transcription, HIV DNA enters CD4 cell's nucleus and integrates with host's DNA via Integrase enzyme
- binds to integrase active site and inhibits strand transfer step of HIV DNA integration
- well tolerated (humans don't have integrase); SE: weight gain, insomnia (rare)
- elvitegravir must be taken with food; rest with or without
- DDIs: polyvalent cations chelate INSTIs (Ca Mg Al Fe); separate antacids/supplements 6 hours on either side)
  - DTG and BIC with metformin: DTG 1.8-fold ↑ metformin AUC; BIC 39% ↑metformin AUC

raltegravir: 400mg bid or 2x600mg HD tabs qd
elvitegravir: 150mg + 150c qd with food; only nonPI that requires boosting*
dolutegravir: 50mg qd; only INSTI that you can give another 50mg q12h later (wide therapeutic index); benign ↑SCr 0.14; high barriers to resistance; metformin interaction*
bictegravir: 50mg qd, only available in Biktarvy (BIC/FTC/TAF); high barriers to resistance; metformin interaction*

Entry/Attachment
- not first or second line; generally reserved for Multi Drug Resistant Strains of HIV (MDRS-HIV); oral IV SC routes

maraviroc: CCR5 antagonist, 300mg po bid; must do CCR5 tropism assay (phenotypic assay of host CD4 cell; if don't have CCR4, don't use MVC); SE: rash, cough, fevers, infection, (URIs)
ibalizumab: post-attachment mab; 2mg IV qd then 800mg q2wk; only approved for MDRS-HIV
fostemsavir: gp120 attachement inhibitor; newest approval; 600mg bid; only approved for MDRS-HIV
enfuvirtide: fusion inhibitor; 90mg sc bid; SE: significant injection site rxns (bruise, nodules, induration, itch); ND, fatigue

PK enhancers
ritonavir: previously discussed 3A4 inhibitor; substrate of 3A4 and 2D6
cobicistat: 3A inhibitor; 150mg qd in combo with PI or EVG; pure PK enhancer (no HIV activity)
  - can cause benign ↑SCr* (stop if SCr ↑>0.4); if ≤0.4 consider SCr as modifier before calculator CrCl (i.e., if ↑SCr 0.3, subtract 0.3 from all future SCr before calc CrCl on cobicstat)

Single-Tablet Regimen (STR)
• Atripla ® (FTC/TDF/EFV), not rec'd 1st line • Biktarvy ® (BIC/FTC/TAF) • Complera ® (FTC/TDF/RPV) • Delstrigo ® (3TC/TDF/DOR)
• Dovato ® (3TC/DTG) • Genvoya ® (FTC/TAF/EVG/c) • Juluca ® (DTG/RPV) • Odefsey ® (FTC/TAF/RPV) • Stribild ® (FTC/TDF/EVG/c)
• Symfi/SymfiLo ® (3TC/TDF/EFV), not rec'd • Symtuza ® (FTC/TAF/DRV/c) • Triumeq ® (DTG/ABC/3TC) • Trizivir ® (ZDV/3TC/ABC), not recommended at all

Combinations
• Combivir ® (3TC/ZDV), not rec'd anymore • Descovy ® (FTC/TAF) • Epzicom ® (ABC/3TC)
• Evotaz ® (ATV/c) • Kaletra ® (LPV/r) • Prezcobix ® (DRV/c) • Truvada ® (FTC/TDF)

Recommended Regimens
INSTI + 2 NRTIs
  - Biktarvy (BIC/FTC/TAF)
  - Triumeq (DTG/ABC/3TC)

- Tivicay (DTG) + [Descovy (FTC/TAF) or Truvada (FTC/TDF) or Epzicom (ABC/3TC)]
- Isentress (RAL) + [Descovy or Truvada or Epzicom]

INSTI + 1 NRTI (optional)
- Dovato (DTG/3TC); only when VL <500,000, HBV negative, and genotypic testing has been done showing full susceptibility

Alternative Regimens

PI boosted + 2 NRTIs
- Symtuza (FTC/TAF/DRV/c)
- DRV/c or DRV/r or ATV/c or ATV/r + 2 NRTIs

INSTI boosted + 2NRTIs
- Genvoya (EVG/c/FTC/TAF)
- Stribild (EVG/c/FTC/TDF)

NNRTI + 2 NRTIs
- Delstrigo (DOR/3TC/TDF)
- DOR + FTC/TAF
- Atripla (EFV/FTC/TDF) or EFV + FTC/TAF; typically not started, continued if patients are resistant to changing therapies

Nuke Sparing Regimens

INSTI + NNRTI
- Juluca (DTG/RPV); never initial therapy; only as switch therapy once VL is undetectable ≥6mo on prev regimen

INSTI + PI
- typically used during extensive NRTI resistance or intolerance
- DRV/c or DRV/r + DTG or RAL
- ATV/c or ATV/r + DTG or RAL

Other considerations
- DHHS guidelines recommend that resistance and tolerance (side effect profile) guide therapy
- weight gain issue? try switching to INSTI-free regimen; TAF associated with more weight gain in combo with INSTIs over TDF
- TAF generally preferred over TDF due to decreased renal and bone toxicities
- pill burden: STRs better adherence, less hospital; therefore simplify regimens to reduce medication inadherence, therapeutic failure, and resistance

Pregnancy
- therapeutic goals: prevent transmission of HIV (primarily by suppression mother's VL); prevent birth defects/harm to fetus
- NRTI backbone = ABC/3TC or TDF/FTC (TAF not enough preg data yet)
- PIs historically used, associated with preterm delivery; ATV/r qd or DRV/r bid
- INSTIs DTG associated with NTD if mother is on during conception or early on in pregnancy, however low incidence and great toleratbility = still used; DTG qd or RAL bid
- NNRTIs are not preferred

PrEP

Truvada (FTC/TDF)
Descovy (FTC/TAF) male only

PEP

Opportunistic Infections

• What's the bug? • Primary prophylaxis? • Symptoms/diagnosis • Treatment and side effects medications

Pneumocystis Pneumonia
Bug: neumocysttis jirovecii, ubiquitous fungus; morbidity/mortality in PLWH
Prophylaxis: when CD4 <200 or CD4<14%; stop when CD4>200 for ≥3mo
SMX/TMP SS or DS **once daily**
Sx: fever, cough, SOB, chest, fatigue
Dx oxygen desat on exertion, Xray infiltrates
Tx: start ART within 2 weeks
mild-mod: **SMX/TMP DS 2 tabs TID for 21 days** [alt: dapsone+TMP, primaquine+clinda, atovaquone]
mod-severe: SMX/TMP IV in 3-4 div doses, may switch to PO with clinical improvement [desens allergy, IV pentamidine, PO prim+IV clinda) (CS based on severity)
SE:
SMX/TMP: rash (SJS), allergy, NVD, photosensitivity, nephrolithiasis/crystalluria (take with water)
dapsone: hemoglobin decrease, hemolytic anemia (when G6PD deficiency)
atovaquone: NVD, HA, insomnia, rash, myalgia, fatigue

Toxoplasma Gondii Encephalitis
Bug: Toxoplasma gondii, protozoan parasite, cause focal enceph, rarely disseminated, can be reactivated; have HIV-neg person change cat litter; avoid raw meat
Prophylaxis: PLWH CD4 <100 and seropositive for Toxoplasma IgG; stop CD4>200 for ≥3mo or CD4 100-200 and HIV VL=UD for 3-6mo
SMX/TMP DS qday [alt dapsone+pyrimethamine+leucovorin qd or atovaquone+/-(pyrimethamine+leucoverin) qd
Sx: HA, confusion, fever, focal neuro deficits, seizures - leucovorin is used to prevent hematologic toxicity of pyrimethamine
Dx: anti-toxoplasma IgG antibody, head CT, CSF analysis
Tx: start ART within 2-3 weeks
pyrimethamine 200mg po once followed by pyrimethamine 50-75mg (60kg) + sulfadiazine 1000-1500mg q6h + leucovorin 10-25mg qday
SE:
pyrimethamine: leukopenia, pancytopenia, thrombocytopenia, hematuria, anorexia, vomit, skin rash (SJS rare)
sulfadiazine: HA, insomnia, arthralgia, nephrolithiasis, anemia, rash (SJS rare)
leucovorin: NVD fatigue, lethargy, anorexia, alopecia

Disseminated Mycobacterium Avium Complex
Bug: Mycobacterium Avium Complex (MAC) group of non-TB mycobacterium that is ubiquitous in environment
Prophylaxis: no longer rec'd in patients who immediately start ART; if CD4 <50 and ART deferred/not suppressed
azithro 1200mg qwk or clarithro 500mg bid [alt macrolide allergy: rifabutin 300mg qd]
Sx: fatigue, fever, wt loss, diarrhea, abd pain, hepato/splenomegaly, lymphadenopathy
Dx: isolated mycobacterial blood culture; labs show anemia, increase ALP (normal bili AST), increase serum lactate dehydrogenase
Tx: start ART immediately; tx finished when 12mo, no s/s MAC disease, sustained CD4 >100 ≥6mo
clarithromycin 500mg bid or azithromycin 500-600mg qd + ethambutol 15mg/kg qd [alt macrolide allergy: rifabutin 300mg qd]
SE:
azithro: NVD, abd pain
clarithro: NVD, abd pain, headache, rash, C. diff
ethambutol: optic neuritis (frequent ophthalmic exams required*), hepatotox, rash, dizziness, HA, NV, hyperuricemia
rifabutin: rash, urine discolor, neutropenia, SJS, thrombocytopenia, C. diff

Cryptococcal Meningitis
Bug: Cryptococcus neoformans, sometimes Cryptococcus gattii; are opportunistic fungus; Cryptococcal meningitis caused by disseminated infection
Prophylaxis: not rec'd d/t low incidence of cryptococcal antigenemia (3-4% CD4 <100); can't avoid exposure, neoformans in soil
Sx: fever, HA; altered mental status, neck stiffness, cranial nerve deficit; sometimes cutaneous manifestations
Dx: CSF test for cryptococcal antigen via LP
Tx: delay ART until at least induction phase is finished to reduce risk of IRIS
induction 2 weeks: liposomal amphoB 3-4mg/kg IV qd or amphoB deoxycholate 0.7-1mg/kg qd (if renal dysf risk low) + flucytosine 25mg/kg po qid or IV qd
consolidation (neg CSF, clinical improvement) 8 weeks: fluconazole 400mg **PO/IV** once daily
maintenance: fluconazole 200mg PO qday ≥12mo; may stop when CD4>100 for ≥3mo, VL UD and asymptomatic
SE:
liposomal amphotericin B: anaphylaxis, infusion rxns, HTN, tachy, edema, chills, insomnia, rash, itch, NVD
amphotericin B deoxycholate: all above + nephrotoxicity*
flucytosine: cardiotoxicity, ataxia, confusion, fatigue, rash, TEN, NVD, abd pain, nephrotox, hepatotox
fluconazole: QTc prolongation, HA, N

Cytomegalovirus
Bug: dsDNA herpesvirus, cause invasive disease retinitis, colitis, CNS; caused by reactivation
Prophylaxis: not rec'd
Sx: retinitis (vision changes floaters, flashing lights, decreased FOV); GI (odynophagia, wtloss, abd pain, D, hematochezia)
Dx: CMV viremia, ophthalmic exam (retinitis), mucosal ulcerations (colitis), biopsy;
Tx: if dx with CMV retinitis hold ART until tx completed (reduce IRIS uveitis)
retinitis: ganciclovir/foscarnet intravitreal + valganciclovir 900mg po bid x14-21d → maintenance valganciclovir 900mg qday
coilitis: ganciclovir IV 5mg/kg q12 until malabsorption resolved then valganciclovir 900mg PO bid x21-42d → maintenance: not indicated unless relapse
SE
valganciclovir/ganciclovir: HA, HTN, insomnia, blood dyscrasias, nephrotoxicity, NVD

Histoplasma capsulatum
Bug: Histoplasmosis fungal infection, common endemic mycosis; causes pulmonary disease and rarely meningitis; soil bird/bad shit, acquired inhalation, reactivate
Prophylaxis: PLWH CD4 <150 avoid soil, chicken coops, caves; not rec'd unless CD4 <150 and high occupational risk/hyperendemic area
  itraconazole 200mg PO qday
Sx: fever, fatigue, wt loss, hepatosplenomegaly, cough, chest pain, dyspnea (50% cases have respiratory complaints), oral/skin lesions
Dx: antigen detection in blood, urine, bronchoalveolar lavage fluid (BAL), CSF or antigen/antibody CSF = meningitis
Tx: start ART immediately
  induction (mod-severe/disseminated): liposomal amphoB x2wk or until clinical improvement
  maintenance/less severe disseminated: itraconazole 200mg PO tid x3d, then bid for ≥12mo (may use vori/fluc)
  meningitis: liposomal amphoB 4-6weeks followed by itraconazole 200mg PO tid ≥12mo
SE:
  itraconazole: ND, HA, rash (caution 3A4 inh)

Esophageal Candidiasis
Bug: Candida albicans, most common AIDS-defining illnesses; occurs CD4 <100; C. dubliniensis, C. glabrata (azole resistance), C. tropicalis can cause disease
Prophylaxis: not rec'd
Sx: retrosternal burning, odynophagia, thrush
Dx: treat on sx, if no response 7 days, visual endoscopy can give definitive dx
Tx: start ART immediately
  fluconazole 100-400mg PO/IV qd x 14-21d (can use itra solution 200mg qd)
  chronic suppressive therapy not rec'd unless CD4 <200 with severe/frequent bouts of esophageal candidiasis

Cryptosporidiosis
Bug: Cryptosporidium protozoan parasite; transmitted through water, chlorine resistant, also person-person
Sx: water diarrhea, NV, intestinal cramp; severity inversely proportional to CD4 count; should test with acute/chronic diarrhea
Dx: oocysts in stool/tissue; modified-acid fast stain, ELISA
Tx: start ART immediately
  nitazoxanide 500-1000mg bid x14d + optimized ART
  supportive oral/IV rehydration
  general population can treat with nitazoxanide 500mg q12h x 3d

Coccidiomycosis
Bug: Coccidiodes immitis, soil fungus; pulmonary infection that mimics CAP; can cause meningitis, liver/lymph node involvement
Tx: don't delay ART (IRIS infrequent)
  mild: fluconazole/itraconazole
  severe: amphoB +/- triazole

Baronella
Bug: Bartonella henselae or B. Quintana; cat scratch disease, trench fever, bacteremia, endocarditis, CNS disease, bacillary angiomatosis
Tx: start ART unless ophthalmic infection then delay until tx finished
  doxycycline +/- gentamicin or rifampin

AIDS Defining Illnesses
Kaprosi Sarcoma : rare cancer, caused by Kaposi sarcoma-ass herpes (KSHV); start ART asap, radiation/surgery/chemo
Progressive Multifocal Leukoencephalopathy (PML): focal demyelinating disease caused by John Cunningham (JC) virus in immunocomp pt; JC 80% inf world
  - cognitive and vision changes, limb paresis, ataxia, seizures Tx: start ART asap
Invasive Cervical Cancer: PLWH and low CD4 higher risk of persistent oncogenic HPV; screen at dx then q12mo/3yr; dx via PAP-smear; Tx: immunize
B-cell Lymphoma: PLWH and low CD4 have higher risk of B-cell lymphomas; DLBCL PEL most common (sx night sweats, wt loss); Hodgkins can occur not AIDS-def
HSV: PLWH who have HSV1/2 likely to experience severe HSV flares or chronic ulcers lasting month; Tx: chronic suppression therapy high doses: valacyc 500bid
Varicella/Zoster: PLWH greater risk for severe complications (pneumo, enchphalitis, HZ ophthalmicus); Tx: immunize

Ceutics

Most antiretroviral agents are prone to PK DDIs because they are substrates (victim) as well as inhibitors or inducers (perpetrator) of CYP enzymes and drug transporters

Gastric acid-reducing causing ↑pH: antacids, PPIs, H2RAs
- chelation reaction occurs with polyvalent (Al Mg, etc)
- some drugs have pH-dep solubility
  - weak bases (↑solubility and dissolution rates at low pH = ↓absorption at gastric pH >4); these mostly ART
  - weak acids (↓solubility and dissolution rates at low pH = ↑absorption at gastric pH >4)

INSTIs BIC DTG EVG RAL: chelation ↓absorption
PI ATV pH-dependent solubility = ↓absorption
NNRTI RPV pH-dependent solubility = ↓absorption
Therefore:
- antacids: separate administration with ART by 2-4 hours
- H2RAs: administer 4 hours before or 12 hours after ART
- PPIs: avoid use with ATV and RPV

<u>CYP-mediated DDIs</u>
- high first-pass CYP-mediated metabolism:
  - CYP inhibition = ↑ oral bioavailability
  - CYP induction = ↓ oral bioavailability
- extensive liver CYP-mediated metabolism
  - CYP inhibition = ↑ exposure
  - CYP induction = ↓ exposure

RTV: inhibitor: 3A4+++ 2C8/2D6++ inducer: 2C19+++ 2C9/2B6/1A2++
COBI: inhibitor: 3A4+++ 2D6++

<u>Transporter-mediated DDIs</u>
- intestine, liver, kidney
inhibit transporter, ↑Cp

TAF/TDF OAT1/3 substrate in kidney

https://www.hiv-druginteractions.org/
http://hivinsite.ucsf.edu/interactions
https://hivclinic.ca/drug-information/drug-interaction-tables/

<u>Clinically Relevant</u>
ATV/c ↑ ticagrelor but ↓clopidogrel ticag 3Asub, clop prodrug; avoid ticag, avoid clopidogrel (unless no alt)
ATV/c DRV/c ↑prava/rosuva exposure via OATP1B as cobicistat inhibit this use lowest effective dose of statin
ATV/c DRV/c ↑simva/lova via 3A4/2D6sub and transporters OATP1B and P-gp; ATV/DRV inhibit 3A4 OATP1B P-gp avoid concomitant use
ATV/c DRV/c ↑metformin via substrate OCT2/MATE1 (renal elim) as cobicistat MATE1 inhibitor reduce dose
Anticonvulsants ↓NNRTI/PI/INSTIs exposure via their induction of CYP and UGTs avoid coadmin, use alt
Cyclosporin ↑bictegravir via P-gp substrate and cyclo inhibits P-gp
Bictegravir/DTG ↑ dofetilide via substrate OCT2/MATE1 avoid use

Invasive Fungal Infections

Histoplasmosis

Path: spores become airborn from bird/bat feces and contaminated soil, inhaled fungal spores can cause pulmonary histoplasmosis; disease is disseminated to other organs via blood/lymphatics is rare (mostly immunocomp); 90% of residents in endemic region have been exposed and have asymptomatic colonization

- acquired via inhalation of spores, not contagious
- primarily pulmonary disease: can mimic TB, but cann occur in CNS, GI, skin

- Ohio, Mississippi valleys

Clinical presentation:

Diagnosis

- culture: blood, bronchioalveolar lavage (BAL), CSF, tissues; difficult to obtain in subacute/acute pt; may take 6 weeks to grow
- antigen: enzyme immunoassay (EIA) is the fastest; performed urine, serum, BAL, CSF
- antibody detection: takes 2-6 weeks to develop Abs, cannot be used to dx during acute infection and in immunocomp

Treatment

mild to mod, acute pulmonary histoplasmosis: treatment unnecessary; consider if symptoms ≥1 month

- itraconazole 200mg tid x3d, then 200mg bid for **6-12 weeks**

mod to severe pulmonary histoplasmosis:

- lipid Ampho B IV (3-5mg/kg) for 1-2wk followed by itraconazole 200mg TID x3d, then 200mg BID for total **12 weeks**
- methylprednisolone 0.5-1mg/kg for 1-2 weeks rec'd with hypoxemia and resp distress

chronic cavitary pulmonary histoplasmosis:

- itraconazole 200mg TID x3d, then 200mg BID for total **18-24 months**
  - therapeutic monitoring recommended after two weeks, goal random level >1 mcg/ml

progressive disseminated histoplasmosis:

- outside lungs, to other organs like liver/sleep (hepatosplenomegaly), occurs 3weeks after; ↑LFT, LDH, ferritin, yeast, granulomas; fatal untreated
- treatment same as mod to severe except for **12 months** or until resolution of s/s/labs

CNS histoplasmosis:

- liposomal Ampho B IV (5mg/kg) for 4-6 weeks followed by itraconazole 200mg TID x3d, then 200mg BID for at least **12 months**

prophylaxis itraconazole 200mg qday

- in HIV with CD4 <150 cells/ml in hyperendemic areas (incidence >10 cases/100 patient years) - duration until CD4 >150
- immunocompromised taking TNFα (infliximab): must receive prophylaxis
- SOT, BMT: if histo <2yrs they may need prophylaxis during immunosupp phase; if chest CT nodules, antigen test in urine/serum 1-32, then yes during immunosupp
  - if had histo, now need SOT, monitor antigen q2-3mo, CT, blood cultures

Blastomycosis

Path: natural reservoir not fully known (common in horses and dogs); treatment not always necessary
- acquired via inhalation
- causes asymptomatic pulmonary disease in most people affected; can spread to skin, bone, bladder, kidney, prostate, testes, etc.
- acute infection presents with non-specific respiratory s/sx (cough, fever, sputum, chest pain, SOB) and indistinguishable from other causes of pulm infection
- chronic blastomycosis/pneumonia may present like TB
- Ohio, Mississippi valleys, Canada, Midwest, bit of south

Clinical presentation:

Diagnosis
- culture: gold standard, sputum, BAL, CSF, tissues
- antigen: EIA fast, not specific nor sensitive, cross-reactive with histo
- histopathology testing sensitivity 50-90%

Treatment

mild to mod pulmonary OR disseminated blastomycosis:
- itraconazole 200mg TID x3d, then 200mg BID for 6-12 months; in patients with osteoarticular disease, duration at least 12 months
- serum itra drawn after 2 weeks to ensure exposure

mod to severe pulmonary OR disseminated blastomycosis:
- lipid Ampho B (3-5mg/kg) for 1-2 weeks followed by itraconazole 200mg TID x3d, then 200mg BID for **6-12 months** (can use Ampho B deoxycholate)

CNS blastomycosis
- lipid Ampho B IV (5mg/kg) for 4-6 weeks followed by oral triazole (fluconazole, itraconazole, voriconazole) for at least **12 months** and resolution of CSF abnormalities

immunosuppressed: lifelong itraconazole 200mg qday if immunosuppression cannot be reversed or if relapsed on appropriate therapy

Coccidioidomycosis (Valley Fever)

Path: inhalation of spores that circulate in air after contaminated soil and dust are disturbed/stirred; grows best in soil after rainfall; disperse during hot, dry times
- California

Clinical presentation:

Diagnosis:
- antibody: EIA very good sensitivity and specificity; combines IgM IgG; takes weeks to months
- culture: sputum or BAL grows in 2-7 days
- antigen PCR urine/serum, only positive in pt with extensive disseminated disease

Risk factors:

Treatment

asymptomatic w/o immunosuppression: treatment not likely needed

symptomatic pulmonary cavity: if severe/immunocompromised, can consider Ampho B initially; oral fluconazole or itraconazole + possible surgical removal

extrapulmonary soft tissue: oral fluconazole or itraconazole (Ampho B considered if refractory)

bone and joint: severe cases Ampho B initially with transition to oral azole eventually; nonsevere use oral azole

cocci meningitis: fluconazole or itraconazole, typically for lifetime treatment (if refractory, increase azole dose, switch, or initiate intrathecal Ampho B)

SOT or hematopoietic cell transplant (HCT): duration 6-12 months
- clinically stable: fluconazole 400mg qday
- very acute and/or rapidly progressing or disseminated: ampho until stable then fluconazole 400mg qday

biological response modifiers: fluconazole for 12 months; IV ampho based on severity

HIV: if CD4 <250, therapy duration until >250

pregnancy:
- 1st trimester: IV ampho
- 2nd/3rd trimester: azole (fluc/itra)
- meningeal 1st: intrathecal ampho
- meningeal 2nd/3rd: fluc/itra

Aspergillosis invasive pulmonary: voriconazole minimum 6-12 weeks

allergic bronchopulmonary aspergillosis (ABPA): itraconazole (2nd vori/posa)

asllergic aspergillosis sinusitis: sinus washings, INCS, azoles

Candidemia: echinocandin (caspo or mica); alt or transition to fluconazole

C. glabrata higher-dose fluconazole or voricon

lipid ampho B alt for echinocandins/azoles if intolerant, limited avail, resistance

Community Acquired Viral Infections

Identify at-risk populations for the development of HSV, VZV, CMV
Have a general understanding of how HSV, VZV, CMV may commonly manifest - HSV1, HSV2, VZV are alpha subtype - CMV beta subtype
Explain the mechanisms of action and resistance of the various antiviral agents used in the management of HSV, VZV, CMV
Recommend an appropriate therapeutic regimen (including drug, route, dose, frequency, and duration) for the management of HSV, VZV, CMV

Herpes Simplex Virus (HSV)
HSV1 oral, latency in trigeminal ganglion (near ear), reactivation face/lip HSV2 genital; latency sacral ganglion, reactivation in genital area
Clinical presentation: prodromal tingle/itch; blister, ulcerative; shedding, can be asymp; canker sore differs in no prodromal, non-fluid filled
- primary infection: often subclinical without lesions, inoculation and replication then dormant
- secondary reactivation: risk factors stress/fatigue, immunocomp, kidney disease; HSV2 reactivate more frequently 4-5x/yr; 98% subclinical shedding genital area
Diagnosis: physical exam; PCR assay swab of lesion; cultures uncommon as hard to grow
Transmission: skin-skin contact (sexual), HSV1 not considered STD; cannot spread inanimate objects
Treatment: episodic (treat each episode), intermittent supp (start AVT before known triggers), chronic suppression (ongoing use in certain immunocomp)
Other severe manifestations:
- Eye HSV: common cause of corneal blindness from HSV1 reactivation - HSV encephalitis: different than meningitis - visceral HSV from viremia

<u>Antiviral Therapy</u>
acyclovir, valacyclovir, famciclovir DOC HSV; max benefit started within 72h, similar efficacy and safety (SE: NVD)
- acy/valacy: high doses renal dysfunction (rare); CNS effects (agitation, halluc, confusion, seizure, encephalopathy) reported
- IV acyclovir: *crystalluria and renal tubular damage; admin over 1hr; renal dysfunction
- foscarnet preferred alternative drug in HSV drug resistance; cidofovir also an option

Topical
acyclovir 5% cream (Zovirax) ap sp 5x/d x4 days (less effective than systemic)
acyclovir 5% + HC1% (Xerese) ap sp 5x/d x5d
penciclovir 1% (Denavir) ap sp q2h x4d (less effective than systemic, less practical freq)
N-docosanol 10% (Abreva) ap sp 5x/d until healed up to 10 days (OTC)
Others: Protectants: Zilactin gel (benzyl alcohol, propylene glycol); Zinc oxide/glycine cream Analgesia: benzocaine qid, lidocaine/prilocaine

Varicella Zoster Virus (VZV)
- when first infected with varicella, you get chickenpox; becomes dormant in dorsal root of ganglia; anyone who had chickenpox is at risk for shingles via reactivation of varicella virus
- 3+ dermatomes is disseminated zoster; complications: pigmentation changes, scarring, superinfections, postherpetic neuralgia; ophthalmic involvement
- spread VZV infection to those who've never had varicella; direct contact with fluid from the vesicles/aerosolization; shingles should cover lesions and avoid contact until dried/crusted
- prevention: Shingrix recombinant, non-live, inactivated vaccine; including those who've had Zostavax
- VZV drugs: acyclovir less active, resistance seen in HIV/immunosupp therapy; again foscarnet preferred and cidofovir alternative

Virus, Duration	**acyclovir**	**valacyclovir**	**famciclovir**
HSV, acute or recurrent oral (5-10 days) genital (7-10 days)	400mg po tid 200mg po 5x/d	1g po bid (cold sore: 2g po bid x1d)	250mg po tid 500mg po bid
HSV: extensive, disseminated, or severe step down to PO to complete 7-10 days	5mg/kg IV q8h	--	--
HSV: suppressive therapy indefinitely, reassess periodically	400-800mg po bid-tid	500mg-1g po qd (or 500mg bid)	500mg po bid
VZV: localized 7 days; can extend 7-10 days in immunosupp	800mg po 5x/d	1g po tid	500mg po tid
VZV: extensive cutaneous involvement step down to PO to complete 10-14 days	10mg/kg IV q8h	--	--

Cytomegalovirus (CMV)
- spread via bodily fluids, transplantation, blood transfusions; 50% by 40yo; causes primary infection than remains dormant until reactivated; most common congenital CMV (fatal)
- risk factors: immunocomp; CD4 <50, previous OIs, high plasma HIV1 >100,000 copies/ml; SOT D+/R-; DMT D-/R+
- often subclinical sx/fever; one of causes of mononucleosis (EBV most common); congenital CMV CNS/sensory impairments
- reactivation manifestations: reitinitis, colitis, esophagitis, pneumonitis, neurological disease, hepatitis

CMV Therapy Approaches
Pre-emptive therapy: initiate antivirals if CMV DNA is detected in blood (CMV infection); utilized in immunocomp high risk end-organ; duration upon resolution of CMV DNA in blood
Definitive treatment: initiation in response to biopsy/ophthalm exam proven CMV reached end-organ; rare for non-immunocomp; duration based on CMV DNA in blood and s/s

CMV antivirals: ganciclovir IV 5mg/kg q12h, valganciclovir 900mg PO q12h, foscarnet IV 90mg/kg q12h, cidofovir IV 5mg/kg qwk, intravitreal foscarnet and ganciclovir
Toxicities ganciclovir: neutropenia, thrombocytopenia foscarnet: nephrotoxicity, electrolyte wasting; CNS toxicity cidofovir: nephrotoxicity, given with probenecid high doses

CMV treatment regimens
pre-emptive for viremia or CMV infection: oral valganciclovir (IV ganciclovir if unable to absorb)
CMV retinitis: oral valganciclovir (sight-lesions consider intravitreal inj; dual IV ganc/fosc for refractory)
CMV colitis: IV ganciclovir (better absorption = diarrhea), can switch to oral valganciclovir upon sx resolution
CMV pneumonitis: valganciclovir

CMV Resistance: biggest risk factor is ganciclovir/valganciclovir use >6weeks
- UL97 (viral kinase) mutation: prevents phosphorylation of ganciclovir - UL54 (DNApol) mutation: evolves following Ul97 but could occur with foscarnet exposure

1. if valganciclovir used, ensure adequate absorption (IV if poor)
2. switch to foscarnet and obtain geno/pheno data (if not severe CMV, consider high dose ganciclovir)
3. assess genotype
   - no mutation: regular ganciclovir dosing; optimize host factors, IV if poor abs
   - UL 97 ≤5 fold GCV EC50: high dose ganciclovir; consider foscarnet mono if end-organ/severe disease or if c/f GCV induced toxicity
   - UL 97 >5 fold GCV EC50: full dose foscarnet
   - UL54 mutation: ganciclovir (R): foscarnet - foscarnet (R): CDV, if susceptible - foscarnet+CDV: foscarnet + high-dose ganciclovir

CMV prophylaxis
- HIV pt: not rec'd in low CD4 counts; after CMV reitinits tx, maintain/secondary prophylaxis used to prevent blindness; consider dc when CD4>100 for 6mo
- SOT: valacyclovir in mod-high risk SOT recipients
- bone marrow transplantation*: letermorvir (only active CMV) in mod-high risk BMT recipieints; these pt at risk for HSV/VZV, MUST be on other antivirals (acy, vala, valgan)

<u>Summary</u>
HSV, VZV, and CMV are three of the eight human herpes viruses (HHVs)
All are associated with a primary infection followed by latency/dormant phase
Reactivation can occur in various patient populations; CMV being most limited to the immunocompromised patient population
HSV-1, HSV-2, and VZV are alpha-HHVs that often present as vesicular lesions and remain latent in sensory neurons
CMV is a gamma-HHV that replicates more slowly and remains latent in lymphocytes and tissues
Antiviral mechanisms are crucial for a clinical pharmacist to understand and interpret in order to identify appropriate therapy for resistant HSV, VZV, or CMV
Acyclovir, valacyclovir, and famciclovir are recommended antiviral therapies for the management of HSV and VZV; however, route/dose/duration vary based on virus (HSV vs VZV) and location (oral vs genital vs systemic)
CMV can be treated via pre-emptive or definitive therapy, with ganciclovir or valganciclovir as first line therapy
Foscarnet is most frequently recommended for suspected acyclovir-resistant HSV and VZV, and for ganciclovir-exposed/resistant CMV
Antivirals for HSV are well tolerated with few reported ADRs, while foscarnet and cidofovir can be very nephrotoxic
CMV prophylaxis is often utilized in SOT and BMT patients, although primary prophylaxis is not recommended in HIV/AIDS patients

COVID-19

Recall the route of transmission and risk factors for acquiring COVID-19
Explain measures that can be taken to help prevent the spread of COVID-19
Describe the clinical presentation of COVID-19, including typical signs and symptoms, risk factors for serious disease, and potential complications
Summarize the pharmacol characteristics (including MoA, dose, indication, adverse effects, monitoring parameters) and clinical data (including ACTT-1/duration trials) for remdesivir
Using knowledge of the NIH guidelines and patient-specific characteristics, recommend appropriate pharmacologic therapy with remdesivir and/or dexamethasone

isolation: measures taken when someon is infected (COVID confirmed) to keep away from others
- asymptomatic dc isolation after 10 days after positive test
- symptomatic dc isolation at least 10 days since symptom onset (24h w/o fever), improving sx
- hospitalized patients at least 10-20 days after symptom onset (24h w/o fever), improving sx, retesting not required

quarantine: measures taken when someone has been exposed to (COVID not confirmed); keep away from others

Prevent spread: 6ft, cover cough/sneeze tissue throw away, stay home when sick, wear mask, don't touch eyes/face, clean/disinfect, wash hands 20seconds
Risk factors: ≥65yo Cancer CKD Lung disease (smoking, COPD) Heart disease (HF, CAD, cardiomyopathy) SOT Severe obesity (BMI≥40) Pregnancy Sickle cell T2DM
Testing
RT-PCR*: high sensitivity and specificity; other NAATs available (RT-LAMP) false negs up to 5 days
antigen (rapid) tests: high specificity, less sensitive than NAATs; cheap, quick; best for early in course of symptomatic infection
serologic testing: not rec'd as sole basis of dx nor to determine immunity to SARS-CoV-2 (may take 21d or longer after sx onset for Abs to be detectable)

Severity of Illness
Asymp: no sx but tests positive for SARS-CoV-2 using virologic test
Mild: sx present; no SOB, dyspnea, or abnormal chest imaging
Mod: SpO2 ≥94% on room air sea level; clinical/radiographic evidence of LRTI
Severe: SpO2 <94%, PaO2/FiO2 <300, RR>30, or lung infiltrates>50%
Critical: respiratory failure, septic shock, and/or multiple organ dysfunction

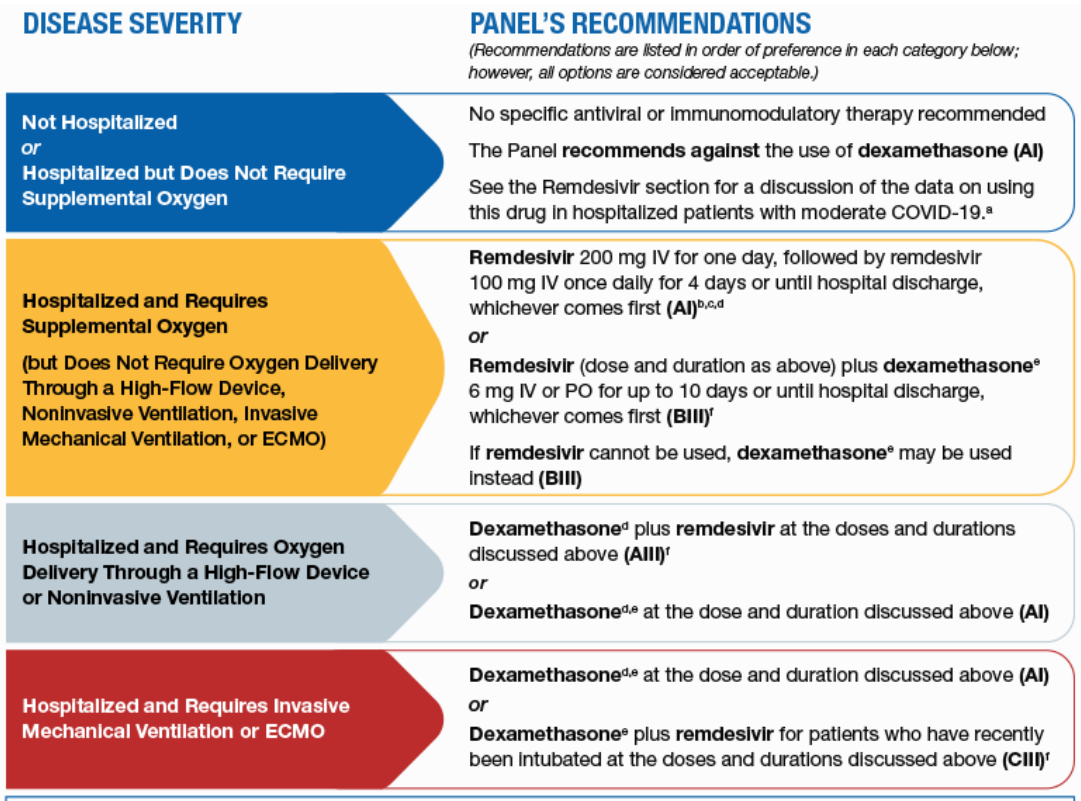
Supportive care
- mild/mod: fluids, antipyretics, supplemental oxygen, VTE prevention
- severe/critical: hemodynamic support (norepinephrine, steroids); ventilatory support (nasal cannula, high-flow HFNC preverred over noninvasive positive pressure NIPPV), mechanical ventilation (low tidal volume preferred), extracorporeal membrane oxygenation (ECMO); renal replacement therapy (CCRT preferred over IMD)

Mild-Moderate "supportive care"

Severe - conventional nasal cannula
- remdesivir 5 days
- remdesivir+dexamethasone 10 days
- remdesivir+dexa not studied in trials, theoretically p
- if dexa n/a, pred/methylpred/hydrocort okay
- dexameth mono no preferred d/t delayed viral clear

Severe - high-flow/noninvasive ventilation
- remdesivir+dexamethasone 10 days

Critical - invasive mechanical ventilation or ECMO
- if remdesivir mono started, but progresses to mechanical ventilation or ECMO occurs, dexameth should be added and remdesivir continued to comp



DISEASE SEVERITY	PANEL'S RECOMMENDATIONS (*Recommendations are listed in order of preference in each category below; however, all options are considered acceptable.*)
Not Hospitalized *or* **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulatory therapy recommended The Panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.[a]
Hospitalized and Requires Supplemental Oxygen (but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)	**Remdesivir** 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)**[b,c,d] *or* **Remdesivir** (dose and duration as above) plus **dexamethasone**[e] 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)**[f] If **remdesivir** cannot be used, **dexamethasone**[e] may be used instead **(BIII)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	**Dexamethasone**[d] plus **remdesivir** at the doses and durations discussed above **(AIII)**[f] *or* **Dexamethasone**[d,e] at the dose and duration discussed above **(AI)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d,e] at the dose and duration discussed above **(AI)** *or* **Dexamethasone**[e] plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**[f]

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

[a] The Panel recognizes that there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate COVID-19 (e.g., a patient who is at a particularly high risk for clinical deterioration). However, the Panel finds the data insufficient to recommend either for or against using remdesivir as routine treatment for all hospitalized patients with moderate COVID-19.
[b] Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[c] The Panel recognizes there is a theoretical rationale for initiating remdesivir plus dexamethasone in patients with rapidly progressing COVID-19.
[d] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical

remdesivir (Veklury)
- FDA approved October 22, 2020
- MoA: SARS-CoV-2 nucleotide analog RNA polymerase inhibitor; chain term after 3 more nucleotides added

indication: tx COVID-19 in adult/ped (≥12yo ≥40kg)
dose: 200mg on day 1, followed by 100mg q24h to complete total of 5-10 days
ADEs: GI sx, transaminitis, increased prothrombin time (PT), hypersensitivity
Monitor*: AST/ALT, SCr, PT at baseline and on therapy; not rec'd if eGFR <30, consider dc if ALT >10x ULN
DDI: substrate 3A4, OATP1B1, P-gp; inhibitor of 3A4, OATP1B1/3, MATE1; in vitro antagonism with hydroxychloroquine
Special pop: okay for pregnancy; ped <12yo or weighing 3.5-40kg emergency use auth (EUA)

Adaptive COVID-19 Treatment Trial (ACTT-1)
- multinational, randomized, double-blind, placebo-controlled trial (NIH)
- hospitalized ≥18yo with COVID-19 and 1 or more of following: pulmonary infiltrates, SpO2 ≤94%, require supplmental oxygen, require mechanical ventilation/ECMO
- primary endpoint: time to clinical recovery for 10 days vs. placebo
- results: *benefit most pronounced in patients who required oxygen supplementation but not HFNC, NIPPV, mech vent, ECMO; greater benefit if RDV initiated within 10d of sx onset
Duration study (5v10d): endpoint: clinical study at day 14; result: no difference in oxygen support at day 14; more serious ADEs in 10-day group

Immunomodulators: dexamethasone RECOVERY trial: lower mortality, lower risk of progression to mechanical ventilation in dexameth arm
bamlanivimab: EUA 11/9/2020; MoA neutralizing IgG1 monoclonal Ab directed against spike protein of SARS-CoV-2; 700mg IV single dose; ADE GI HA dizzy, infusion, hypersens, pruritis
  - NOT for patients who are hospitalized or require oxygen supplementation; monitor for severe rxns
Insufficient data for blood-derived products
Convalescent plasma: passive immunization through transfusion of blood from person who has recovered and developed Abs; unclear benefit

Summary
SARS-CoV-2 is a respiratory virus transmitted primarily through respiratory droplets that causes the disease COVID-19
Patients who are older and have certain underlying diseases are at higher risk for severe manifestations of COVID-19
Supportive care, antiviral therapy with remdesivir, and adjunctive therapy with corticosteroids are treatment modalities recommended by the NIH guidelines
Emerging therapies such as neutralizing antibodies and vaccines are under development and will be available in the coming weeks to months
Spread of the virus can be prevented through basic measures (e.g., social distancing, masking, hand hygiene), isolation of confirmed cases, and quarantining after exposure

Antivirals Pcol

Drugs for DNA Virus Influenza Hepatitis B Hepatitis C Antiretrovirals

I. Families of Viruses
II. Viral Transmission and Life Cycles
III. Immune Surveillance Against Viruses
IV. Antiviral Therapy
  A. Immunologic Therapy
    a. Adaptive
    b. Innate
  B. Chemotherapy
    a. DNA Viruses
    b. RNA Viruses
    c. Retroviruses

DNA Viruses

Hepadnaviruses	Hepatitis B (**HBV**)
Herpes Viruses	Varicella Zoster (**VZV**) (aka Shingles, Chicken Pox)
	Herpes Simplex (**HSV**)
	Cytomegalovirus (**CMV**)
POX Viruses	Small Pox
Adenoviruses	Sore throat, Conjunctivitis
Papilloma Viruses	Cervical Cancer, Skin Warts

RNA Viruses

Orthomyxoviruses	Influenza A, B, C
Paramyxoviruses	Respiratory Synctial Virus (**RSV**), Measles, Mumps
Flaviviridae	Hepatitis C (**HCV**)
& Arboviruses	Zika, Dengue, Yellow Fever, Encephalitis
Coronaviruses	SARS, COVID-19
Rhabdoviruses	Rabies
Picornoviruses	Colds, Meningitis, Poliomyelitis, Hepatitis A
Arenaviruses	Meningitis, Lassa Fever
Rubella Virus	German Measles
Ebolavius	Ebola

RNA Retroviruses

Human Immunodeficiency Virus (**HIV-1** & **HIV-2**) → AIDS
HTLV-1 → T-Cell Leukemia

Modes of Viral Transmission
1. Human to Human: Most viral infections
2. Animal to Human: Rabies (dogs, bats), Yellow fever (mosquitos), Encephalitis (Arthropods)
3. Food/Water to human (e.g. Hepatitis)
4. Syringes/equipment to humans (e.g. hepatitis, HI)

Study List for Antiviral Pharmacology, D. Hoyt

Know general considerations, biochem, structure, infection process; details of life cycles of DNA viruses, non-retroviral RNA viruses and Retroviruses (p. 5-14)
Infection process: 1. Adsorption 2. Penetration & Uncoating 3. Replication, Transcription & Translation 4. Assembly 5. Release of New Virus 6. Secondary Infection of Other Cells

Know the roles of antigen presenting cells, helper T cells, cellular and humoral immunity and interferon in the reaction to infection (summarized on p. 16-17)
- Antigen Presenting Cells (macrophages, others) take up and digest antigens
- processed antigen presented on cells of surface in a complex with MHC; contact induces APC to secrete IL-1
- T helper cells produce IL-2
- IL-2 activates T helper cells to make cytokines including interferon
- these promote cellular and humoral immunity

cellular immunity: destroys virus-infected cells, which can reduce virus multiplication in the body
- interferon activates cytotoxic T cells, Natural Killer cells, and macrophages to seek and kill virus-infected cells AND induces resistance of other host cells to virus

humoral immunity: T helper cells contacts B cell holding correct antigen with MHC; T help produces other cytokines that stimulate b cell to reproduce, make Abs

Know how antibodies could affect a virus (p. 18)
- binds antigen, can neutralize/antagonist it
- Fc stem allows cells to recognize antigen-antibody complex so it can be phagocytosed and destroyed (there's an Fc receptor on host cell)

Know passive vs active immunization (adaptive system), and the characteristics of each these types of immunization (p. 19-20)
Active (vaccine): administration of antigen to induce cellular and humoral immunity; takes time to develop; use is prophylaxis; ideal prevents disease, low freq admin, nontoxic
- mechanism: memory T and B cells activate when exposed to authentic virus antigens; ceullar and humoral immunity activated
  - cellular: killer cells remove virus infected cells
  - humoral: antibodies coat virus, induce opsonization/phagocytosis by macrophage/neutrophils/others; immunoglobulins interfere with adsorption if react with surface antigen

Passive: inject antibody coats virus, induces opsonization/phagocytosis; use is treatment and prophylaxis; rapid onset; duration 1-3mo protection;
Which? active preferred but can combine passive and active to immediately suppress disease and enhance future immunity

Know palivizumab (Synagis) (p. 22) for respiratory syncytial virus. You do not need to know any other specific vaccines or passive agents.
MoA: passive immunization; monoclonal Ab binds to viral F protein on its surface; prevents viral entry into cells
Spectrum: respiratory syncytial virus (RSV, RNA virus); RSV most common cause of bronchitis and pneumonia in children
Dose: IM qmo during RSV season (Oct-Apr); reduces hospitalization 55%

Know which immune systems produce interferons (INF) (p. 16, 23). Know the innate immune system recognition systems that stimulate production of interferons (p. 23). You are NOT responsible knowing specific subtypes of toll receptors or how they signal.
Innate system; Type I INF produced by
1) plasmacytoid dendritic cell precursors (or natural interferon producing cells); Toll-like receptors and viral glycoproteins that interact with viral components
2) most normal cells via dsRNA receptors: Protein Kinase R (PKR and Retinoic acid-Inducible Gene 1 (RIG-1)

interferon action: circulates and activates interferon receptors on other cells which induces expression of many genes that promote resistance to many viruses

Know the antiviral actions of interferon, top of p.24 and the antiviral spectrum. You should remember that interferons can induce flu-like symptoms. You do not need to know the other toxicities. Interferon-α only one currently used as a therapeutic
Actions of INF-induced genes against viruses include inhibition of viral penetration/uncoating, transcription, translation, protein glycosylation required for processing/maturation of virus; interferons also activate Killer cells (NK and CD8+ T-killers) that may attack viruses-infected cells
Spectrum: most RNA viruses, most DNA viruses, retroviruses; interferons can cause flu-like symptoms; Uses: HepB/C, HepD (chronic, not acute), papilloma virus (warts)

Know the general difficulties in viral chemotherapy (p. 25)

Know the considerations regarding spectrum of activity of antiviral agents, p. 27.
Drugs generally work on viruses of one genome type; however some drugs work on multiple classes of virus (but more side effects)
1. drugs against herpes virus (DNA) 2. drugs against influenza and hepC (RNA, nonretroviral) 3. drugs against HIV-1 HIV-2 (RNA retroviruses)

Know the genome types of the viruses named on p. 28.
DNA: HSV, VZV, CMV, HBV RNA: Influenza, RSV, HCV Retroviruses: HIV-1 HIV-2

For spectrum of action of drugs or classes, Know if they work on DNA, RNA or Retroviruses.
For drugs used against DNA viruses, know if they work better on herpes viruses or on cytomegalovirus
For drugs used against RNA viruses, know if they work on influenza A or B
Know the drugs that work on Hepatitis B and HIV. Other instructors may ask about other drugs used for hepatitis B.
The exam will not ask about selectivity for HIV-1 or 2, but you need to know which base analogs work on Hepatitis B and HIV (summary on p 90).
Know which drugs work on more than one of DNA, RNA or Retroviruses

HCV targets exploited:
1. Protease: nonstructural protein NS3-4A, a serine protease
   - a heterodimer of N-term serine protease domain of NS3 protein (catalytic subunit) and NS4A cofactor (activation subunit, membrane bound)

- cleaves HCV polyprotein precursor at four sites; produces several enzymes and structural proteins for virus

2. RNA polymerase: nonstructural protein NS5B, an RNA-dependent RNA polymerase responsible for the complete copy of the RNA viral genome
3. Nonstructural protein NS5A: helps in viral replication, and assembly in some way

Drugs for DNA Viruses

1. Inhibitors of viral DNA polymerase and/or Hepatitis B Reverse Transcriptase

Base analogs: acyclovir (Zovirax, Sitavig), valacyclovir (Valtrex), famiciclovir (Famvir), peniciclovir (Denavir), ganciclovir (Cytovene), cidofovir (Vistide), entecavir (Baraclude, Entaliv), tenofovir, telbivudine (Tyzeka), lamivudine (3TC, Epivir), adefovir (Bispom, Preveon); topical: vidarabine, idoxuridine, trifluridine

Non-Base analog polymerase inhibitor: foscarnet (Foscavir)

2. Inhibitor of Viral Assembly by blocking DNA packaging: letermovir (for CMV)

3. Drug affecting RNA: ribavirin (Virazole)

4. Inhibitor of HSV attachment: docosanol

5. Miscellaneous (for warts): Immune Modulator imiquimod (Aldara); for papilloma virus: podofilox (Condylox)

<u>acyclovir (Zovirax, Sitavig), valacyclovir (Valtrex)</u>

^valacyclovir is L-valine ester prodrug that is better absorbed; has cross-resistance

MoA: phosphorylated by viral thymidine kinase >> human kinase; cellular enzymes make triphosphate increases accumulation in infected cells

- triphosphate inhibits viral DNA polymerase; competes with dGTP; lacks 3'OH; when incorp into DNA it terminates chain, irreversibly inactivates viral DNA pol

MoA summary: selective metabolic activation to acyclovir triphosphate gives you analog of dGTP and is competitive inhibitor of the use of dGTP by viral DNA polymerase (selectively over human); if incorporates into new DNA synthesized strand, has no 3'OH to add more bases down the line, thus terminating chain; additionally, the 3'OH-lacking terminus of the synthesized strand of DNA, that structure itself is an inhibitor of viral DNA polymerases; furthermore, the enzyme in the viral cell that converts acyclovir to acyclovir monophosphate (Viral Thymidine Kinase) has higher expression so increases activation of acyclovir

Spectrum: higher potency HSV/VZV > CMV

Resistance: 1. deficient/mutant viral thymidine kinase; 2. mutant viral DNA polymerase

Use: agent of choice HSV-1, HSV-2, VZV

Tox: well tolerated

<u>penciclovir (Denavir), famciclovir (Famvir)</u>

^famciclovir is inactive prodrug (di-acetylated at -OH) converted to penciclovir

MoA: activated in same way as acyclovir; 100x less potent at inhibition of viral DNA polymerase, but accumulates to higher conc and has longer HL

- do not cause complete chain termination (two hydroxyl groups), but slow down polymerization after incorporation

Spectrum: same as acyclovir

Resistance: same as acyclovir; effective in acyclovir-resistant cases where altered DNA polyermase or other factors may be the cause; however, thymidine kinase resistance mechanisms will result in cross-resistance

Use: same as acyclovir

Tox: same as acyclovir

<u>ganciclovir (Cytovene), valganciclovir (Valcyte)</u>

^valganciclovir is L-valyl ester prodrug

MoA: in herpes: viral thymidine kinase performs first phosphorylation, then cellular kinases make di- and triphosphate as for acyclovir

- in <u>CMV</u>: UL97 Kinase phosphorylates the drug first
- ganciclovir triphosphate competitively inhibits dGTP on DNA polymerase, inhibits elongation after incorporation into DNA (by CMV DNA polyermase UL54)
- 10x greater concentrations of activated drug in CMV-infected cells vs. unaffected cells (fyi: oral valgan similar conc to iv ganciclovir)

Spectrum: higher potency against CMV > HSV/VZV

Resistance: mutation of viral DNA polymerase; CMV: UL97 mutations; thymidine kinase mutations (cross-resistance with acyclovir)

Use: prophylaxis and treatment of CMV; especially useful in transplant patients

Tox: 1. myelosuppression (15-40%) neutropenia at 2 weeks; 2. CNS side effects (5-15%); 3. teratogenesis not ruled out, potential genotoxicity

<u>cidofovir (Vistide)</u>

MoA: pyrimidine analog of cytosine; made into active diphosphate by cellular enzymes

- cidofovir diphosphate competitively inhibits use of dCTP by viral DNA polymerase (8-600x preference vs. human polymerase)
- since cidofovir does not require a first kinase, it can be used for ganciclovir-resistant CMV as this due to mutation of UL97

Spectrum: higher potency against CMV > HSV

Resistance: mutant viral DNA polymerase (not kinases)

Use: cytomegalovirus (CMV), particular ocular retinis in HIV (immunocomp)

Tox: dose-limiting nephrotox: proteinuria (80-90%); acidosis; skin lesions can be caused by topical form; NV, fever, asthenia, possible carcino/terato

FYI: idoxuridine spectrum: herpesviruses, poxviruses

FYI: trifluridine spectrum: HSV-1, HSV-2, CMV

<u>foscarnet (Foscavir)</u>

MoA: 1. does not require activation by viral kinase; 2. inhibits viral DNA polymerase >> human DNA polymerase; 3. also inhibits HIV reverse transcriptase

Spectrum: affects DNA and retroviruses

Resistance: 1. mutant herpes DNA polymerase; 2. mutant CMV DNA polymerase ("UL54" as opposed to UL97 kinase); 3. mutant HIV reverse transcriptase

Use: restricted bc of high frequency toxicity; 1. ganciclovir-resistant CMV (inhibits UL54 DNA polymerase); 2. HSV-resistant to acyclovir/ganciclovir; 3. adjunct AIDs

Tox: 1. nephrotoxicity (50%); 2. hypocalcemia (arrthymias, seizures); 3. mutagenic, birth defects seen in animal studies

<u>letermovir (Prevymis)</u>

MoA: blocks DNA terminase function; stops packaging/viral assembly

Use: prophylaxis in stem cell transplant patients; also works well in CMV resistant to base analogs

Drugs for Hepatitis B

Base analogs that inhibit Hepatitis B reverse transcriptase

tenofovir disoproxil fumarate (Viread), tenofovir alafenamide (Vemlidy)

MoA: antihepadnaviral; reverse transcriptase inhibitor; nucleotide (anti-HBV)
- analog of adenosine, a nucleotide; similar to adefovir
- tenofovir alafenamide hydrolyzed and phosphorylated to tenofovir diphosphate
- tenofovir diphosphate inhibits HIV and Hepatitis reverse transcriptase and viral DNA polymerase; competes with dATP and causes chain termination

Spectrum: Hepatitis B, HIV, HSV

Use: HIV and HBV (discontinuation can lead to flare up of HBV infection)

Tox: low frequency but consequential hepatotoxicity/lactic acidosis could occur

adefovir (Hepsera), adefovir dipivoxil

MoA: antihepadnaviral; reverse transcriptase inhibitor; nucleotide (anti-HBV)
- analog of adenosine (dipivoxil metabolized to adefovir); phosphorylated adefovir diphosphate
- inhibits viral DNA polymerase and reverse transcriptase; terminates chian if incorporated in DNA

Spectrum: Hepatitis B, HSV, HIV

Resistance: occurs with high frequency over several years of HBV therapy; not used alone
- may cause development of HIV resistance in patients with unrecognized/untreated HIV infection

Use: trials were for HepB; anti-HIV action requires high doses, trials halted due to toxicity
- limited to chronic HepB in adults with evidence of active viral replication and elevated hepatic enzymes

Tox: fatal cases of lactic acidosis and hepatomegaly with steatosis reported in combo with other antiretrovirals

lamivudine (3TC, Epivir)

MoA: antihepadnaviral; reverse transcriptase inhibitor; nucleoside (anti-HBV)
- cytosine analog; phosphorylated to triphosphate
- competes with dCTP to inhibit reverse transcriptases and incorporated into viral cDNA causing chain termination

Spectrum: Hepatitis B, HIV

Resistance: develops with high frequency over several years of HBV therapy
- reemergence of infection due to resistance causes danger liver disease, therefore not used alone

entecavir (Baraclude, Entaliv)

MoA: antihepadnaviral; reverse transcriptase inhibitor; nucleoside (anti-HBV)
- analog of guanosine; cellular kinases phosphorylate to make entecavir triphosphate
- competes with dGTP to inhibit viral DNA polymerase and reverse transcriptase; incorporated in DNA leading to chain termination

Use: Hepatitis B first line

Resistance: has lower frequency of resistance relative to other base analogs
- not effective vs. HIV and may induce HIV-resistance in chronic Hep B patients that also have HIV, so not rec'd in patients with HIV

telbivudine (Tyzeka)

MoA: antihepadnaviral; reverse transcriptase inhibitor; nucleoside (anti-HBV)
- thymidine analog (L-enantiomer); phosphorylated to active triphosphate
- competes with TTP to inhibit reverse transcriptase activity of HepB
- no effect on HIV

Use: treatment of chronic Hepatitis B

Resistance: occurs at high frequency during HBV therapy; not rec'd first-line and generally not used alone
- cross-resistance with other HBV drugs may develop (ex. patients failing lamivudine may also be resistant)

Tox: CNS (fatigue 13%); neuromuscular/skeletal: 1. myopathy (aches/weakness with increased serum creatine kinase) occurs within weeks; 2. peripheral neuropathy (weakness/pareasthesia/leg pain) occurs within weeks to months; treatment discontinued if confirmed; concurrent interferons is CI as neuropathy incr
- lactic acidosis and hepatomegaly with steatosis reported, including fatal cases
- acute exacerbation of HepB may occur upon discontinuation

Targeting RNA Metabolism

ribavirin (Virazole)

MoA: antihepaciviral, nucleoside (Anti-HCV); basically inhibits production and use of RNA; ribose-base analog
- phosphorylated by cellular enzymes; RMP inhibits GTP synthesis by inhibition of inosine 5'-phosphate dehydrogenase
- RTP inhibits usage of mRNA interfering with GTP capping of 5'end of mRNA
- inhibits RNA polymerase decreasing mRNA and protein synthesis

Spectrum: unusual since it's broad spectrum; affects many DNA and RNA viruses

Use: RNA viruses: HepC in combo with interferon; RSV

Tox: aerosol breathing difficulties; systemic: hemolysis, bone marrow suppression; teratogenic

Drugs for Influenza

Viral Influenza (RNA Virus)

amantadine, rimantadine

MoA: prevent uncoating of influenza A virus after viral entry into host cell and release
- drugs bind and inhibit action of viral M2 protein ion channel; inhibits acidification of internalized vescicle
  - 1. inhibits dissociation of ribonucleoprotein complex, 2. inhibits acid-induced hemagglutinin conf change that would allow binding of virus to cell receptors

Spectrum: influenza A only
Use: seasonal prophylaxis (70-90% effective); treatment within 48h flu onset may dec duration; prophylactic immunocomp/high risk
Resistance: inherent resistance rare but drugs rapidly select for M2 mutants in 30% subjects; resistant forms replace original virus in 2-3 days; cross-resistance
Tox: GI N, CNS (onsomnia, mood), high doses seizures arrythmias

oseltamivir, zanamivir, peramivir

MoA: neuramidase inhibitor; prevents release of virus, aggregates on cell surface and fail to spread within respiratory tract
- neuraminidase an enzyme known to cleave the budding viral progeny from its cellular envelope attachment point (neuraminic acid) just prior to release

Spectrum: influenza A B
Resistance: hemagglutinin and/or neuraminidase mutants
Use: decrease days of illness by 1-2 days (peramivir restore body temp in 12h); prophylaxis decrease flu incidence 60-70%
Resistance: seasonal H1N1 resistance increasing; other influenza A subtypes remain sensitive
Tox: oseltamivir NV, peramivir D, zanamivir dry powder inhaler nasal/throat bronchospasm

baloxavir marboxil (Xofluza)

MoA: inhibits Cap-dependent endonuclease activity of RNA polymerase
- prevents virus from stealing 5' ends of host RNAs that are used to start viral transcripts
- stops viral RNA production

Spectrum: influenza A B (works in influenza resistant to classic agents)
Resistance: 10% of subjects developed resistant enzyme after single dose
Tox: low freq diarrhea nasopharyngitis

Drugs for Hepatitis C

Hepatitis C (RNA Virus)

Hepatitis C Serine Protease (HS3-4A) Inhibitors

--simeprevir, paritaprevir, grazoprevir, glecaprevir, voxilaprevir
MoA: inhibition of protease prevents assembly of HCV; block Toll and RIG-1 induction of interferon
Use: comb with pegylated interferon-α and ribavirin; not used alone
Spectrum: HCV specific
Resistance: may occur due to changes in protease target

Hepatitis C Polymerase (NS5B) Inhibitors

MoA: NS5B, an RNA-dependent RNA polymerase responsible for complete copy of RNA viral genome
sofosbuvir (Sovaldi): prodrug; metabolite dUTP analog is incorporated in RNA and terminates chain, inhibiting HCV replication
dasabuvir: non-nucleoside inhibitor of NS5B; binds at sites other than nucleotide site to allosterically inhibit NS5B

NS5A Inhibitors

--ledipasvir, ombitasvir, daclatasvir, elbasvir, pibrentasvir, velpatasvir
NS5A protein required for HCV replication and assembly; unknown how it works but 4 functional domains and disrupt some aspect of NS5A
MoA: disrupt replication and assembly
Spectrum: HCV specific

Combinations

—

Antiretrovirals

NRTIs (Nucleoside and Nucleotide Reverse Transcriptase Inhibitors)	
abacavir (ABC)	Ziagen
didanosine (ddI)	Videx
emtricitabine (FTC)	Emtriva
lamivudine (3TC)	Epivir
stavudine (d4T)	Zerit
tenofovir af (TAF)	Vemlidy
tenofovir df (TDF)	Viread
zidovudine (ZDV, AZT)	Retrovir

NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors)	
doravirine (DOR)	Pifeltro
efavirenz (EFV)	Sustiva
etravirine (ETR)	Intelence
nevirapine (NVP)	Viramune
rilpivirine (RPV)	Edurant

INSTIs (Integrase Strand Transfer Inhibitors)	
dolutegravir (DTG)	Tivicay
elvitegravir (EVG)	Vitekta
raltegravir (RAL)	Isentress
bictegravir (BIC)	in Biktarvy

PIs (Protease Inhibitors)	
ritonavir (RTV) PK boosting	Norvir
saquinavir (SQV)	Invirase
indinavir (IDV)	Crixivan
fosamprenavir (FPV)	Lexiva
atazanavir (ATV)	Reyataz
darunavir (DRV)	Prezista
nelfinavir (NFV) non-peptidomimetic	Viracept
tipranavir (TPV) non-peptidomimetic	Aptivus
lopinavir (LPV)	in Kaletra

Misc (Entry Inhibitors)	
Fusion inhibitor enfuvirtide (T-20)	Fuzeon
CCR5 antagonist maraviroc (MVC)	Selzentry
Attachment inhibitor fostemsavir	Rukobia
Post-attachment inhibitor ibalizumab	Trogarzo

PK enhancers	
ritonavir (RTV/r)	Norvir
cobicistat (c)	Tybost

Fixed-dose combinations		
abacavir-lamivudine	Epzicom	(ABC/3TC)
abacavir-lamivudine-zidovudine	Trizivir	(ABC/3TC/ZDV)
bictegravir-emtricitabine-tenofovir af	Biktarvy	(BIC/FTC/TAF)
darunavir-cobicistat-emtricitabine-tenofovir af	Symtuza	(DRV/COBI/FTC/TAF)
dolutegravir-abacavir-lamivudine	Triumeq	(DTG/ABC/3TC)
dolutegravir-lamivudine	Dovato	(DTG/3TC)
dolutegravir-rilpivirine	Juluca	(DTG/RPV)
doravirine-lamivudine-tenofovir df	Delstrigo	(DOR/3TC/TDF)
efavirenz-emtricitabine-tenofovir df	Atripla	(EFV/FTC/TDF)
elvitegravir-cobicistat-emtricitabine-tenofovir af	Genvoya	(ECF/TAF or EVG/COBI/FTC/TAF)
elvitegravir-cobicistat-emtricitabine-tenofovir df	Stribild	(ECF/TDF or EVG/COBI/FTC/TDF)
rilpivirine-emtricitabine-tenofovir af	Odefsey	(RPV/FTC/TAF)
rilpivirine-emtricitabine-tenofovir df	Complera	(RPV/FTC/TDF)
tenofovir af-emtricitabine	Descovy	(TAF/FTC)
tenofovir df-emtricitabine	Truvada	(TDF/FTC)
zidovudine-lamivudine	Combivir	(ZDV/3TC)
lopinavir/ritonavir (PI combination)	Kaletra	(LPV/r)
darunavir-cobicistat (PI combination)	Prezcobix	(DRV/COBI)
atazanavir-cobicistat (PI combination)	Evotaz	(ATV/COBI)

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Highly Active Antiretroviral Therapy (HAART): combination of 3 drugs from at least 2 different classes

HIV uses CD4 and CCR5 or CXCR4 to attach to cells
- HIV gp120 attaches to CD4 T helper cells via binding of CD4 molecule and to receptors for cytokines that are recognized by the Th cell, CCR5 and CXCR4
  - CCR5/CXCR4 function to cytokine signaling to T helper cells
- both CD4 and CCR5/CXCR4 are needed for optimum binding and internalization; mutations in both compies of CCR5 are resistant to HIV infection
- CD4/CCR5 receptors are on Th lymphocytes, monocytes/macrophages, neurons in CNS
- steps in binding
  1. gp120 binds CD4 on target cell
  2. causes conformational change in gp120 so it binds cell CCR5/CXCR4 coreceptor
  3. induces HIV gp41 to fold back on itself which is critical for fusion with the target cell

Long Terminal Repeat (LTR) are specialized sequences at each end of genome: 1. used for integration into host genome by viral integrase; 2. in host DNA, LTR seq is recognized by HIV tat protein and host transcription factors (NFkB); this drives transcription of HIV genome in host DNA (essentially promoters of transcription)
AIDS pathogenesis: as HIV replication ↑ CD4 count ↓
- Seroconversion: initial drop in viremia d/t cytotoxic T cells
- HIV evolution: aa changes in virus coat take time to make HIV immunoresistant; able to overwhelm immune system later, destroying Helper cells

Complications of AIDS, main problem: opportunistic infections result from immunodeficiency

Immune Reconstitution Inflammatory Syndrome (IRIS)
successful restoration of immune system may lead to exaggerated immune attack on other microorganisms (~10% of patients, often occurs within about 30d)
inflammation or paradoxical worsening of symptoms of infection can occur; severe cases might be controlled with antimicrobial agent or corticosteroids

NRTIs (Nucleoside and Nucleotide Reverse Transcriptase Inhibitors)

NRTIs (Nucleoside and Nucleotide Reverse Transcriptase Inhibitors)	
abacavir (ABC)	Ziagen
didanosine (ddI)	Videx
emtricitabine (FTC)	Emtriva
lamivudine (3TC)	Epivir
stavudine (d4T)	Zerit
tenofovir af (TAF)	Vemlidy
tenofovir df (TDF)	Viread
zidovudine (ZDV, AZT)	Retrovir

- all resemble nucleosides; activated intracellularly to triphosphates by cellular enzymes
- lack 3'OH necessary for continued cDNA polymerization; RTase makes faulty/incomplete DNA copies of HIV RNA
- generally work on HIV-1 and HIV-2
- can cause hepatic damage, steatosis, lactic acidosis (low frequency but fatal); alcohol enhances risk of hepatic damage
- all NRTIs effective against HIV 1 and 2
  - some agents active against HBV: emtricitabine, lamivudine, tenofovir; tenofovir activity against herpesviruses

Mitochondrial Dysfunction Theroy

Avoid combinations:
  - agents that use identical kinases for activation; agents causing additional toxicities of pancreatitis/sensory neuropathy; similar base analogs

Avoid combinations of NRTIs:- overlapping metabolic activation - overlapping additional toxicities- same analog of a base
  - d4T/AZT (competes for phosphorylation of thymidine kinase, mutually antagonize activation)
  - d4T/ddl (d/t overlapping additional toxicities of sensory neuropathy and pancreatitis)
  - 3TC/FTC (both cytosine analogs, no added benefit in combining, may induce each other's resistance)
  - TDF/ABC (no additive/synergistic activity when used; may increase risk of resistance)

<u>zidovudine (ZDV, AZT, Retrovir)</u>
- first effective anti-HIV drug (1987); thymidine analog
- phosphorylated 1st by cellular Thymidaine Kinase, 2nd by Thymidylate Kinase, 3rd by Nucleoside Diphosphate Kinase
- should not be combined with stavudine (competes for phosphorylation of thymidine kinase, mutually antagonize activation)
- additional Tox: bone marrow suppression (anemia, neutropenia)
- fyi:

<u>stavudine (d4T, Zerit)</u>
- competes with AZT for phosphorylation by thymidine kinase (mutually antagonize activation); AZT and stavudine are also thymidine analogs
- additional Tox: pancreatitis; peripheral sensory neuropathy (15-20%)
- avoid combos: d4T/AZT (…), d4T/ddl (d/t overlapping additional toxicities of sensory neuropathy and pancreatitis)
- fyi:

<u>didanosine (ddl, Videx)</u>
- adenosine analog: triphosphorylated form competes with dATP for incorporation into HIV cDNA
- additional Tox: pancreatitis; painful sensory peripheral neuropathy
- avoid combo: d4T/ddl (…)
- fyi:

<u>lamivudine (3TC, Epivir)</u>
- also inhibits HBV RT; cytosine analog competes with dCTP for incorp into viral cDNA, converted to triphosphate causing polymerase inhibition and chain term
- HBV could reemerge more severely if present when drug discontinued
- avoid 3TC/FTC (both cytosine analogs, no added benefit in combining, may induce each other's resistance)

<u>emtricitabine (FTC, Emtriva)</u>
- cytosine analog; 5'triphosphate also inhibits HBV RTase and weak inhibitor of mammalian DNA polymerase
- HBV could reemerge more severely if present when drug discontinued
- avoid 3TC/FTC (both cytosine analogs, no added benefit in combining, may induce each other's resistance)

<u>tenofovir df (Viread), af (Vemlidy)</u>
- nucleotide analog of adenosine (tide); inhibits HIV and hepatitis RTase and viral DNA polymerase
- Spectrum: both HIV and HBV, herpesviruses
- use: HIV, HBV - pre-exposure prophylaxis of HIV with emtricitabine
- HBV could reemerge more severely if present when drug discontinued
- Tox: hepatotoxicity/lactic acidosis
- fyi

<u>abacavir (ABC, Ziagen)</u>
- pure guanine analog
- effective in children
- hypersensitivity (rash, histaminergic sx requires dc'ing); reinstatement can be fatal (OH, resp distress, death); tests available to predict reaction HLA B5707
- avoid combo: TDF/TAF and ABC (no additive/synergistic activity when used; may increase risk of resistance)

NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors)

- do not require intracellular phosphorylation; do not resemble nucleosides
- bind to reverse transcriptase adjacent to active site; causes conformational change in active site, inhibiting it
- spectrum: HIV-1 only, *not* HIV-2
- cross placenta, present in milk - causes rash (sometimes severe)
- metabolized by hepatic cytochrome P450, resulting in many DDIs (including with protease inhibitors)
- rapid development of resistance when used alone (generally due to mutations in reverse transcriptase)

NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors)	
doravirine (DOR)	Pifeltro
efavirenz (EFV)	Sustiva
etravirine (ETR)	Intelence
nevirapine (NVP)	Viramune
rilpivirine (RPV)	Edurant

nevirapine (NVP, Viramune)

- 1st-gen
- skin rash (16%): sometimes severe/fatal; dose limiting effect in 7% of cases; can be minimized by starting low and titrating over 2 weeks
- special use: prevents transmission from mother to newborn; given to mother at onset of labor, orally to infant within 3 days
- special tox: hepatotoxicity can be fatal

delavirdine (Rescriptor)

- 1st-gen
- skin rash (18-36%); same as nevirapine
- special tox: teratogenic, avoid use in pregnancy
- irreversibly inhibits 3A4 and others

efavirenz (EFV, Sustiva)

- 1st-gen
- crosses BBB
- other tox: skin rash; CNS (50%): due to CNS penetration/distribution: dizziness, HA, insomnia, nightmares, hallucinations; teratogenic, avoid use in pregnancy

etravirine (ETR, Intelence)

- 2nd-gen; maintained activity against some viruses with existing NNRTI resistance mutations
- tox: rash (10-15%) generally stop using if skin rxn occurs even though it might not progress or could decrease; FYI rare SJS
- hepatic damage; fat redistribution (like protease inhibitors), may cause buffalo hump, peripheral wasting with increased abdominal girth

rilpivirine (RPV, Edurant)

- 2nd-gen
- tox: rash (3%); FYI fat redistribution; depression

PIs (Protease Inhibitors)

HIV protease is dimer of two 99aa subunits; each contributes an Aspartic acid to active site; human aspartyl proteases are monomeric and 1000-fold less sensitive
HIV protease cleaves gag-pol polyprotein producing 1. active enzymes (RTase, HIV protease, integrase) and 2. structural proteins (p17, p24, p9, p7)
Original HIV protease inhibitors resemble transition state of cleave sequences of gag-pol (enzymes prefers to cute Phe-Pro in polyprotein); non-peptidics: NFV, TPV
Inhibition of protease prevents maturation of virus

- in combination with reverse transcriptase inhibitors they markedly lower peripheral blood levels of HIV, prolong survival
- not a cure since lowering dose leads to resurgence of HIV blood levels
- most work on HIV-1 and 2 (some may be better against HIV-1)
- orally administered
- resistance: develops quickly when used alone; mutation in protease enzyme of HIV; all transported by PGP MDR-1 resistance, limits BBB penet; cross-resistance
- kinetics: metabolized by hepatic cytochrome P450 leading to DDIs
- tox: GI disturbances (NVD) worse with ritonavir (limits use); causes hyperglycemia/diabetes (CVD risk); causes fat redistribution/hyperlipidemia (CVD risk)
- tox: elevated liver enzymes; possibility of increased bleeding risk for hemophiliacs

ritonavir
GI side effects have reduced its usage, but still used in combinations
- low doses (100-200mg bid) with fewer side effects can be used to inhibit metabolism of other ptoease inhibitors and decreases frequency of their administration

saquinavir
FYI: generally combo with ritonavir

indinavir
10x more inhibition of HIV-1 protease compared to HIV-2 enzyme

fosamprenavir
phosphorylated prodrug of earlier amprenavir with better solubility
- converted to amprenavir by cellular phosphatases, essentially a "slow-release" version of amprenavir
- tox: discontinue if severe rash

PIs (Protease Inhibitors)	
ritonavir (RTV) PK boosting	Norvir
saquinavir (SQV)	Invirase
indinavir (IDV)	Crixivan
fosamprenavir (FPV)	Lexiva
atazanavir (ATV)	Reyataz
darunavir (DRV)	Prezista
nelfinavir (NFV) non-peptidomimetic	Viracept
tipranavir (TPV) non-peptidomimetic	Aptivus

lopinavir
- used in combo with ritonavir (Kaletra)
- tox: pancreatitis, arrythmia

atazanavir
- does not appear to affect plasma lipoproteins
- distinct resistance profile*: no obvious pattern of cross-resistance with other protease inhibitors

darunavir
- combined with ritonavir low dose and taken with food to attain appropriate concentrations

nelfinavir
- non-peptidomimetic
- tox: general see above

tipranavir
- non-peptidomimetic
- appears to bind to HIV protease differently than other peptide based agents
- *HIV strains resistant to other protease inhibitors are often responsive to tipranavir
- coadmin with ritonavir, increases Cp 30-fold (metabolized 3A4)
- tox: diarrhea; hepatotoxicity (6%, dose-dep)
- reports of fatal/nonfatal intracrancial hemorrhage; low freq but dangerous SE should be reserved for pt with resistance to other agents or advanced disease

INSTIs (Integrase Strand Transfer Inhibitors)

- integrase forms complex with viral DNA LTRs
- terminal dinucleotide from each end of viral DNA is removed by endonuclease processing
- viral DNA ends are covalently linked to cellular DNA (strand transfer); this is the stp that is blocked
- MoA: strand transfer in step 3 is antagonized
- Use: effective against HIV-1 and 2
- tox: generally well tolerated; some incidence of insomnia or dizziness

INSTIs (Integrase Strand Transfer Inhibitors)	
dolutegravir (DTG)	Tivicay
elvitegravir (EVG)	Vitekta
raltegravir (RAL)	Isentress
bictegravir (BIC)	in Biktarvy

FYI:

- mutations in strand transfer active site of integrase; some mutations may drive selection; dolutegravir resistance less common
- elvitegravir combo with emtricitabine, tenofovir, cobicstat for HIV-1
  - cobicstat included to raise elvitegravir level by inhibiting CYP3A
- patients who fail raltegravir or elvitegravir have high risk of developing integrase resistance (possible cross-resistance here)

Misc (Entry Inhibitors)

- blocking HIV entry is based on the function of gp120/gp41

Misc (Entry Inhibitors)	
Fusion inhibitor enfuvirtide (T-20)	Fuzeon
CCR5 antagonist maraviroc (MVC)	Selzentry
Attachment inhibitor fostemsavir	Rukobia
Post-attachment inhibitor ibalizumab	Trogarzo

<u>enfuvirtide (T-20, Fuzeon)</u>

- binds HIV gp41 preventing folding and fusion with target cell
  - blocks HIV from entering healthy human immune cells
  - active against strains that have become resistant to already available drugs
  - synthetic peptide corresponding to repeat sequence in HIV gp41
- env gene: synthesis of envelope precursor protein (gp160)
  - gp160 processed by host protease into the two envelope proteins, gp120 and gp41
- enfuvirtide is sequence from HR2 (C-term Heptad repeat)
- MoA: competes with endogenous HR2 for binding to HR1 (N-term Haptad repeat); antagonizes folding of gp41
- use: not used by itself; can reduce amount of HIV in blood; increases CD4 count
- tox: inflammation (drug also binds FMLP chemotaxis receptor on leukocytes); rare but serious pneumonia
- tox: 98% patients develop injection site reactions to varying degrees

<u>maraviroc (MVC, Selzentry)</u>

- disrupts HIV adsorption via CCR5
- binds host cell CCR5 preventing interaction of HIV gp120 with this co-receptor
  - selective, reversible CCR5 coreceptor antagonist; binds to CCR5 and prevents V3 domain of gp120 from binding CCR5; inhibits HIV entry
- tox: skin rash (11%), vomiting, sensitivity to infections (55%)

<u>fostemsavir (Rukobia)</u>

- metabolized to temsavir, binds gp120 preventing CD4-induced conformation change in gp120, prevents subsequent V3 domain binding to to CCR5 or CXCR4
- binds HIV gp120 preventing CD4-induced conformation change in gp120 that would allow association with host cell co-receptors
- tox: hepatic, renal, cardiac (<2% QT high doses)

<u>ibalizumab (Trogarzo)</u>

- an anti-CD4 antibody that disrupts HIV adsorption
- binds host cell CD4, preventing interaction with HIV gp120
  - binds CD4 on T-helper cell, cause conformational change in CD4 that blocks interaction of gp120 and HIV co-receptors; disrupts HIV attachment
- tox: skin rash (5%), diarrhea (8%)