



Central Nervous System

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ICU Sedation

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ICU Problems

- ▶ Agitation, anxiety, delirium
- ▶ Identifying cause can be incredibly difficult
- ▶ Common causes
 - ▶ Pain
 - ▶ Hypoxemia
 - ▶ Hypoglycemia
 - ▶ Hypotension
 - ▶ Withdrawal
 - ▶ Adverse effects
 - ▶ Infection

Non-Pharmacological Interventions

- ▶ First line for problems
 - ▶ Comfort
 - ▶ Appropriately assessing analgesia
 - ▶ Reorientation
 - ▶ Maintaining normal sleep patterns

Sedation

- ▶ Minimal sedation possible
 - ▶ Light sedation
 - ▶ Able to arouse patient
 - ▶ Deep sedation
 - ▶ Patient is unresponsive
- ▶ Choice of sedating agent will vary depending upon situation/tolerability

Sedation Scale Examples

- ▶ RASS (Richmond Agitation-Sedation Scale)
 - ▶ Subjective
 - ▶ Combination of sedation and agitation/combateness level
 - ▶ Ideal score is “0” – alert and calm (+4 combative; -5 unarousable)
- ▶ Sedation Agitation Scale (SAS)
 - ▶ 1-7 (level of agitation (7 is highest, striking out at staff, pulling out IV tubing etc.)
 - ▶ 1 is unarousable
 - ▶ Subjective
- ▶ Brainstem auditory evoked potentials
 - ▶ Objective
 - ▶ Electrodes placed on scalp (measures response to auditory stimulus)

ICU Sedation - Medications

- ▶ Propofol (Diprivan)

- ▶ Mechanism of Action: Binds multiple receptors in the CNS to interrupt neural transmission, including GABA_A, glycine, nicotinic, and M₁ muscarinic receptors
- ▶ Rapid on/offset
- ▶ Dissolved in lipid emulsion
 - ▶ Rare but serious Propofol Infusion syndrome (PRIS)
 - ▶ Hypertriglyceridemia, rhabdomyolysis, acidosis, hypotension, hyperkalemia, arrhythmia, AKI, Liver dysfunction
- ▶ Dose-dependent
 - ▶ Hypotension
 - ▶ Respiratory depression

Benzodiazepines

- ▶ Mechanism of Action: Activate GABA_A receptors in the brain
- ▶ Elderly may be more sensitive to effects
- ▶ Midazolam, lorazepam, diazepam
 - ▶ Midazolam has quickest onset
 - ▶ Lorazepam – contains propylene glycol and may cause toxicity depending upon amount used (monitor serum osmol gap)
- ▶ Tolerance can develop
- ▶ Great choice in status epilepticus

Dexmedetomidine (Precedex)

- ▶ Mechanism of Action: Selective α_2 -receptor agonist with sedative, analgesic sparing and sympatholytic properties
 - ▶ Less respiratory depression than other agents
- ▶ Hypotension
- ▶ Bradycardia
- ▶ Typically patient is more easily arousable

Opioids

- ▶ I.e. Fentanyl
 - ▶ Avoid overusing if possible
 - ▶ Respiratory depression
 - ▶ Can extend mechanical ventilation time
- ▶ Be cautious about tapering down if has been on chronic opioids
 - ▶ Withdrawal can cause agitation
- ▶ If on other agents for sedation, be careful about patient waking up in pain

Delirium

- ▶ Antipsychotics
 - ▶ Drug of choice in delirium
 - ▶ Haloperidol has the most evidence; quetiapine, ziprasidone and other 2nd generation agents; selection of a specific antipsychotic may depend upon adverse effect profile



Insomnia

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Insomnia Concerns

- ▶ Troubles
 - ▶ Getting to sleep
 - ▶ Staying asleep
- ▶ Quality of Life
 - ▶ Motivation
 - ▶ Ability to perform at work/school
- ▶ Short-term
 - ▶ A few weeks
- ▶ Chronic
 - ▶ Months

Non-Drug Interventions

- ▶ 1st Line Therapy
- ▶ Sleep Hygiene
 - ▶ Regular schedule
 - ▶ Snacks/warm milk
 - ▶ Avoiding Caffeine near bedtime
 - ▶ Minimize stimulation before bed
 - ▶ Exercise earlier in the day
 - ▶ Pain
 - ▶ Avoiding other stimulants

Pharmacotherapy

- ▶ Z-drugs
- ▶ Anticholinergics
- ▶ Melatonin
- ▶ Trazodone
- ▶ Benzo's
- ▶ Ramelteon
- ▶ Mirtazapine
- ▶ Suvorexant

Z-Drugs

- ▶ “Z” Drugs – zolpidem (Ambien), zaleplon (Sonata), eszopiclone (Lunesta)
- ▶ Mechanism of Action: Binds to and potentiate the effect of GABA receptors leading to a sedative type effect
- ▶ Fall risk, confusion
- ▶ Risk of dependence
- ▶ Abnormal sleep behaviors
- ▶ Helpful for onset and maintenance
- ▶ Dose restriction on zolpidem – limit to 5 mg, risk of next day impairment at 10 mg

Other Insomnia Agents

- ▶ Ramelteon (Rozerem)
 - ▶ Acts on MT1 and MT2 (melatonin) receptors to help induce sleep
 - ▶ Dizziness, GI side effects
 - ▶ Most beneficial in sleep-onset, not a controlled substance
- ▶ Suvorexant (Belsomra), lemborexant (DayVigo), daridorexant (Quviviq)
 - ▶ Mechanism of Action: Orexin receptor antagonist
 - ▶ CYP3A4 inhibitors can raise concentrations and increase risk for toxicity
 - ▶ CNS SE's, dizziness, abnormal dreams
 - ▶ Controlled substance
 - ▶ Expensive
 - ▶ Helpful for onset and maintenance

Trazodone and Mirtazapine

- ▶ Trazodone (Desyrel)
 - ▶ Lower doses typically used for insomnia (12.5-100 mg) especially in the elderly
 - ▶ Classically considered an antidepressant, but usually only at higher doses
 - ▶ Orthostasis, dry mouth, CNS changes, and priapism (rare) are possible adverse effects
 - ▶ Generally considered to be better tolerated in the elderly than “Z” drugs or anticholinergics
 - ▶ Onset and maintenance
- ▶ Mirtazapine (Remeron)
 - ▶ Often used at low doses for its sedative properties
 - ▶ May cause more activation as doses escalate
 - ▶ A potential option to help with insomnia, weight loss, and mental health disorder like depression or possibly anxiety
 - ▶ See depression section for more information

Melatonin

- ▶ Available OTC
- ▶ Considered “safe” by many patients due to it being a natural product
- ▶ Side effects of dizziness, GI, headache, lingering sedation throughout the day, possibly hyperprolactinemia with higher doses
- ▶ Not great clinical trial evidence of effectiveness, but some patients will swear by it
- ▶ Maybe not a terrible option versus anticholinergics and Z drugs
- ▶ For sedative effect, usual max dose around 10 mg/day
 - ▶ Most patients, target 1-5 mg range
- ▶ <1mg doses for altering circadian rhythm

Anticholinergics

- ▶ Diphenhydramine, doxylamine, doxepin, TCA's
- ▶ Retention
- ▶ Dry eyes
- ▶ Dry mouth
- ▶ Constipation
- ▶ Fall risk
- ▶ Confusion (interacts with dementia meds)
- ▶ Doxepin - evidence in sleep maintenance

Antipsychotics for Sleep

- ▶ Can be sedating
- ▶ Always avoid unless compelling indication
 - ▶ Hallucinations unresolved by other methods
 - ▶ Schizophrenia



Stroke and TIA's

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Types of Stroke

- ▶ Hemorrhagic
- ▶ TIA
- ▶ Ischemic
 - ▶ Local (Atherosclerotic)
 - ▶ Heart (Atrial Fibrillation)

Classic Signs

- ▶ Face drooping
- ▶ One sided arm weakness
- ▶ Slurred Speech
- ▶ Confusion
- ▶ Vision changes
- ▶ Fall

Classic Risk Factors

- ▶ Hypertension
- ▶ Smoking
- ▶ Atrial Fibrillation
- ▶ Diabetes
- ▶ Hyperlipidemia
- ▶ Age
- ▶ Genetics

Prevention of Stroke

- ▶ Manage modifiable risk factors
 - ▶ Hypertension
 - ▶ Smoking
 - ▶ Weight loss
 - ▶ Diabetes
 - ▶ Statins

Options for Long Term Management of Stroke

- ▶ Atherosclerotic
 - ▶ Aspirin
 - ▶ Aggrenox (Aspirin/Dipyridamole)
 - ▶ Clopidogrel
 - ▶ Dual antiplatelet therapy with clopidogrel and aspirin is typically not recommended for secondary prevention of stroke unless there is a cardiac compelling indication (i.e. stenting) or carotid artery stenting
- ▶ Cardioembolic (Atrial Fibrillation)
 - ▶ DOACs
 - ▶ Warfarin
 - ▶ Aspirin

Acute Ischemic Stroke Management

- ▶ Reperfusion
 - ▶ tPA
- ▶ Quicker the better for tPA administration
 - ▶ Best outcomes 90 minutes or less (ideal target is 60 minutes or less)
 - ▶ Good evidence of benefit in 3 hours or less
 - ▶ 3-6 hours range, less evidence
 - ▶ Inclusion criteria <4.5 hours since onset of symptoms and 18 years of age or older

Thrombolytics

- ▶ Alteplase (tPA)
 - ▶ Recombinant tissue plasminogen activator that converts plasminogen to plasmin, leading to fibrin clot breakdown
- ▶ Indications
 - ▶ Acute ischemic stroke with measurable neurologic deficit
 - ▶ Must be given within 4.5 hours of symptom onset (earlier is better)
 - ▶ Requires CT/MRI ruling out intracranial hemorrhage
- ▶ Adverse Effects
 - ▶ Intracranial hemorrhage (most serious)
 - ▶ Systemic bleeding
 - ▶ Angioedema (higher risk with ACE inhibitors)
 - ▶ Hypotension, nausea

Thrombolytics

- ▶ Tenecteplase (TNK-tPA)
 - ▶ Genetically modified tPA with greater fibrin specificity and longer half-life than alteplase.
- ▶ Indications
 - ▶ Acute ischemic stroke as an alternative to alteplase (increasingly used)
 - ▶ Typically given as a single IV bolus.
 - ▶ Most commonly within 4.5 hours of symptom onset or before mechanical thrombectomy.
- ▶ Adverse Effects
 - ▶ Intracranial hemorrhage
 - ▶ Systemic bleeding
 - ▶ Rare hypersensitivity reactions

Exclusion Criteria - tPA

- ▶ History of intracranial bleeding
- ▶ Active bleed/hemorrhage (last 21 days)
- ▶ BP > 185/110
- ▶ Recent head trauma/surgery (3 months)
- ▶ INR >1.7, heparin, or other anticoagulant (including DOACs)
- ▶ Platelets < 100,000
- ▶ Glucose < 50
- ▶ Endocarditis



Psychiatric



Attention Deficit Hyperactive Disorder

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Symptoms

- ▶ Fidgets
- ▶ Constantly moving
- ▶ Can't sit still
- ▶ Forgetful
- ▶ Disruptive behavior
 - ▶ Relationships
 - ▶ School function/learning

Drugs

- ▶ Stimulants (methylphenidate, amphetamines)
- ▶ Atomoxetine
- ▶ Bupropion
- ▶ Central alpha-2 agonists
 - ▶ Clonidine, guanfacine

Selection Considerations

- ▶ Adverse effect profile
 - ▶ Weight
 - ▶ Vitals
 - ▶ Sleep pattern
- ▶ Dosage forms/frequency of dosing
- ▶ Cost
- ▶ Family considerations
 - ▶ Ensure non-drug interventions have been exhausted
 - ▶ Controlled substance

Amphetamine Derivatives

- ▶ Mechanism of Action: Sympathomimetic drugs that stimulate release of norepinephrine and dopamine in the CNS
- ▶ Mixed Amphetamine salts (Adderall, Adderall XR), Dextroamphetamine (Dexedrine), Lisdexamfetamine (Vyvanse)
- ▶ Controlled substances (Schedule 2)
- ▶ Adverse effects
 - ▶ Insomnia, aggression, tics
 - ▶ Weight loss, poor growth
 - ▶ Cardiovascular problems like hypertension and tachycardia
 - ▶ Risk of diversion
 - ▶ Priapism

Dosing Pearls

- ▶ Longer acting preparations can help avoid the ups and downs compared to immediate release formulations
 - ▶ But can cause insomnia if dosed too late in the day
- ▶ Longer acting preps can also help avoid redosing during the school day for children
 - ▶ Adderall duration of action: 4-6 hours
 - ▶ Adderall XR duration of action: 8-12 hours
- ▶ You will often see a dose in early/midafternoon of immediate release as the morning long acting may wear off for some patients
- ▶ Response of stimulants' benefits are usually apparent within an hour or two, whereas other agents may take a while to have an adequate trial
 - ▶ Dose titration can happen fairly quickly with stimulants (every week or so depending upon clinical factors as well)

Methylphenidate

- ▶ Methylphenidate (Concerta, Daytrana, Metadate CD, Methylin, Ritalin), dexamethylphenidate (Focalin)
 - ▶ Mechanism of Action: Inhibits norepinephrine and dopamine reuptake leading to similar effects as amphetamine
 - ▶ Similar side effect profile to amphetamines
 - ▶ Schedule 2 controlled substance

Dosage Form Considerations

- ▶ Dosage forms often juggled to try to find the right medication that gives an adequate response and also lasts an appropriate amount of time without impacting sleep
- ▶ Drug holidays – controversial, often determined on a case by case basis whether patients should take days off or not
- ▶ Daytrana – patch formulation; 9 hours on (10-12 hour duration of action)
- ▶ Ritalin IR duration of action: 3-5 hours
- ▶ Ritalin SR duration of action: 8 hours
- ▶ Concerta duration of action: 10-12 hours

Stimulants

- ▶ Amphetamine salts (Adderall)
 - ▶ Extended release and immediate release
- ▶ Methylphenidate
 - ▶ Capsule, patch, solution, extended release
- ▶ Adverse effect/monitoring
 - ▶ Weight
 - ▶ Cardiovascular
 - ▶ Insomnia

Atomoxetine (Strattera)

- ▶ Inhibits norepinephrine reuptake
- ▶ Non-controlled alternative to stimulants in those who cannot or won't take stimulants
- ▶ Insomnia, GI
- ▶ Rare – risk of liver injury, suicidal thoughts
- ▶ May take a while to see a response which differs from traditional stimulants
- ▶ CYP2D6 inhibitors may increase concentration

Other Agents

- ▶ Bupropion
 - ▶ Avoid in seizure disorder
 - ▶ Non-controlled
 - ▶ Takes a while to work
- ▶ Clonidine, guanfacine
 - ▶ Antihypertensive effect
 - ▶ Rebound hypertension
 - ▶ Non-controlled
 - ▶ Immediate benefit not likely
 - ▶ Fatigue
- ▶ Drug holidays are not appropriate with these agents

Nursing Monitoring

- ▶ Improvement or worsening of ADHD symptoms
- ▶ Height and weight (baseline and ongoing)
- ▶ Signs of misuse, diversion, or dependence (stimulants)
- ▶ Blood pressure and heart rate (baseline and periodically)
- ▶ Mood changes, irritability, anxiety, or agitation
- ▶ Sleep

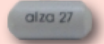
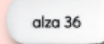
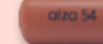
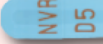
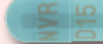
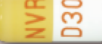
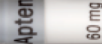
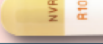
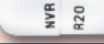
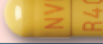
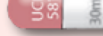
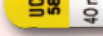
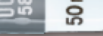
ADHD Dosage Forms Link

<https://adhdmedicationguide.com/>

ADHD Medication Guide*

Methylphenidate Formulations – Long Acting, Oral**

(Capsules and tablets in this section are shown at actual size)

Concerta®†	6-12 Yrs: 18-54mg; SD: 18mg 13-17 Yrs: 18-72mg; SD: 18mg ≥18 Yrs: 18-72mg; SD: 18mg or 36mg	 18mg 	 27mg 	 36mg 	 54mg 	Relexxii® (bioequivalent to corresponding Concerta dosing)		 45mg 
Focalin® XR‡ (dexamethylphenidate)	6-17 Yrs: 5–30mg; SD: 5mg 18 Yrs-Adult: 10–40mg; SD: 10mg (biphasic – 50/50)	 5mg 		 10mg 	 15mg 	 20mg 	 25mg 	 30mg 
Cotempla XR-ODT®¶ (grape flavor)	6-17 Yrs: 8.6–51.8mg; SD: 17.3mg	8.6mg 		17.3mg 	25.9mg 	34.6mg  + 		51.8mg  +
Aptensio® XR‡	6 Yrs–Adult: 10–60mg; SD: 10mg (biphasic – 40/60)	 10mg 	 15mg 	 20mg 	 30mg 	 40mg 	 50mg 	 60mg 
Quillivant XR® 25mg/5mL (5mg/mL) (banana flavor)	6 Yrs–Adult: 20–60mg; SD: 20mg	10mg 2mL  1 Bottle: 300mg 60mL		20mg 4mL  1 Bottle: 600mg 120mL	30mg 6mL  1 Bottle: 900mg 180mL	40mg 8mL  2 Bottles: 600mg 120mL	50mg 10mL  2 Bottles: 750mg 150mL	60mg 12mL  2 Bottles: 900mg 180mL
QuilliChew ER®§ (cherry flavor)	6 Yrs–Adult: 20–60mg; SD: 20mg (biphasic – 30/70)			20mg 	30mg 	40mg 		
Ritalin® LA‡	6-12 Yrs: 10–60mg; SD: 20mg (biphasic – 50/50)	 10mg 		 20mg 	 30mg 	 40mg 		 60mg 
Metadate® CD‡	6-17 Yrs: 10–60mg; SD: 20mg (biphasic – 30/70)	 10mg 		 20mg 	 30mg 	 40mg 	 50mg 	 60mg 

Anxiety

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Assessment

- ▶ GAD-7
 - ▶ 7 questions
 - ▶ Example: Feeling afraid something awful might happen
 - ▶ Scored from 0-3 for each question
 - ▶ Not at all
 - ▶ Several days
 - ▶ More than half the days
 - ▶ Nearly every day
 - ▶ Higher the score the worse
 - ▶ Obviously might not work in our dementia type patients

Acute Treatment

- ▶ Identify underlying cause
 - ▶ Pain
 - ▶ Infection
 - ▶ Hyperthyroid
 - ▶ Medications
 - ▶ Stimulants
 - ▶ Alpha/beta agonists

Medications

- ▶ SSRI's
- ▶ Benzo's
- ▶ Buspirone
- ▶ Other antidepressants
- ▶ Antipsychotics (usually with comorbidities)

SSRI's

- ▶ Won't work quickly
- ▶ Preferred for long term maintenance over benzo's
- ▶ Selection based upon adverse effects

Benzodiazepines

- ▶ Mechanism of Action: Potentiate the effect of the inhibitory neurotransmitter GABA
- ▶ Lorazepam (Ativan), clonazepam (Klonopin), diazepam (Valium), alprazolam (Xanax), chlordiazepoxide (Librium), clorazepate (Tranxene), oxazepam (Serax), temazepam (Restoril), triazolam (Halcion)
- ▶ Ideal for acute relief of symptoms – dependence risk with long term use
- ▶ Side effects similar to alcohol in a pill
 - ▶ Sedation, slurred speech, confusion, fall risk
- ▶ Flumazenil is reversal agent – carries a boxed warning for seizure risk
- ▶ Schedule 4 controlled substance
 - ▶ Avoid in patients with a history of substance use

Benzodiazepines

- ▶ Shorter acting benzo's
 - ▶ Triazolam
- ▶ Intermediate acting
 - ▶ Alprazolam, clonazepam, lorazepam, temazepam, oxazepam
- ▶ Long acting
 - ▶ Diazepam, chlordiazepoxide, flurazepam
- ▶ Notable drug interactions and metabolic breakdown
 - ▶ Opioids (boxed warning – risk of respiratory depression)
 - ▶ Additive CNS depressants (trazodone, H1 antihistamines, etc.)
 - ▶ Diazepam – CYP2C19 and CYP3A4
 - ▶ Alprazolam – CYP3A4
 - ▶ Clonazepam – CYP3A4

Buspirone (Buspar)

- ▶ Mechanism of Action: Bind tightly (strong affinity) for 5-HT_{1A} receptors, but exact mechanism of anxiolytic effect is unknown
- ▶ Advantages
 - ▶ Non-controlled substance
 - ▶ Pretty well tolerated (even in older patients) compared to benzodiazepines
- ▶ Disadvantage
 - ▶ Takes a while to work
 - ▶ Multiple times a day dosing

Antihistamines

- ▶ 1st generation antihistamines
 - ▶ hydroxyzine (Atarax, Vistaril)
 - ▶ Much more sedating and anticholinergic than 2nd generation, but may provide anxiety relief
 - ▶ Sedation of 1st generation antihistamines can be advantageous if patient has trouble sleeping because of symptoms
 - ▶ Alternative in those who have or are at risk of abusing benzodiazepines



Bipolar Disorder

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Bipolar Symptoms

- ▶ Very severe mood swings
- ▶ Mania
 - ▶ High self-esteem (grandiosity)
 - ▶ Way more talkative than normal
 - ▶ Constant changing of topics during conversation (racing thoughts)
 - ▶ Insomnia or just needing less sleep
 - ▶ Interrupts normal life (i.e. work, school, commitments), or others can identify that something is strange
 - ▶ Psychosis
- ▶ Hypomania
 - ▶ Patients experience a higher level of energy and/or and enhanced mood compared to normal, but it is generally not associated with impairment

Bipolar Disorder

- ▶ Very depressed stages
- ▶ Bipolar 1 – have had manic episode(s)
- ▶ Bipolar 2 – haven't had a manic episode (only hypomania)
- ▶ Risk of suicide
- ▶ Often huge social and financial problems
 - ▶ Relationships
 - ▶ Spending sprees with manic episodes
 - ▶ Legal problems
 - ▶ Work problems

Risk Factors

- ▶ Substance abuse
- ▶ Anxiety
- ▶ Post-traumatic stress disorder
- ▶ ADHD
- ▶ Family history

Lithium

- ▶ Target Concentration

- ▶ Acute 0.8-1.2
- ▶ Maintenance 0.6-1.0

- ▶ AE's

- ▶ GI
- ▶ Tremor
- ▶ Slurred Speech
- ▶ TSH
- ▶ Kidney function

- ▶ Drug Interactions

- ▶ NSAIDs
- ▶ Thiazides
- ▶ ACE Inhibitors

Valproic acid

- ▶ Indications - bipolar, seizures, migraines, sometimes used off label for aggressive type behaviors
- ▶ SE's – CNS sedation, GI upset, and lots of unique, rare side effects (reduced platelets, elevated ammonia, hair loss, LFT elevation)
- ▶ Typical target level 50-100
- ▶ Watch interaction with lamotrigine
- ▶ May cause weight gain
- ▶ Multiple dosage forms can have slightly different bioavailability
- ▶ Pregnancy risks

Lamotrigine

- ▶ Sedation, CNS side effects
- ▶ Hallmark RASH side effect – usually when started at too high of a dose or increased too quickly
- ▶ Takes a bit of time (weeks to months) to get to higher doses when titrating appropriately to minimize rash risk
 - ▶ If stopped for a significant period of time, need to start over at low dose and titrate slowly
- ▶ Drug interaction with valproic acid (likely need to reduce dose of lamotrigine)
- ▶ Enzyme inducers (i.e. phenytoin, carbamazepine) can reduce concentrations of lamotrigine in the body
- ▶ Usually best for bipolar patients with predominant depression symptoms

Carbamazepine

- ▶ Not a preferred first line agent in bipolar disorder
- ▶ CNS side effects, GI upset, elevated LFTs, alterations in WBC count, hyponatremia
- ▶ Monitor CBC, LFTs, and sodium (SIADH)
- ▶ Induces multiple CYP enzymes – be on the lookout for reduced concentrations of meds that are metabolized via this pathway (lots of common 3A4 interactions)
- ▶ Considered an auto-inducer – can reduce its own levels
- ▶ Levels aren't as important in treating trigeminal neuralgia (unless signs of toxicity)
- ▶ Steven Johnson's syndrome (SJS) – severe, rare rash is possible
 - ▶ HLA-B*1502 Allele at higher risk for SJS (higher incidence in patients of Asian descent)
- ▶ Usual target levels are 4-12 mcg/mL
 - ▶ Not necessary for trigeminal neuralgia

Antipsychotics

- ▶ Quetiapine – second line option for maintenance
- ▶ Other antipsychotics are options as well for refractory patients
 - ▶ Risperidone
 - ▶ Aripiprazole
 - ▶ Olanzapine
 - ▶ Long acting injectable agents

Bipolar Depression

- ▶ SSRI's
 - ▶ Can induce mania
 - ▶ Avoid monotherapy
 - ▶ Fluoxetine
 - ▶ Often used with mood stabilizer (i.e. Lithium, VPA, Carbamazepine)



Depression

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Depression Risks

- ▶ Suicide
- ▶ Circumstances
 - ▶ Finances
 - ▶ Job Loss
 - ▶ Living alone
 - ▶ Aging
 - ▶ Loss of Family/Friends

Common Diseases That Increase Depressive Symptoms

- ▶ MS
- ▶ Parkinson's
- ▶ Dementia
- ▶ Cancer
- ▶ Hypothyroid
- ▶ Nutritional factors
 - ▶ B12

Antidepressant Pearls

- ▶ Take time to work
- ▶ Selection
 - ▶ Adverse effects
 - ▶ Compelling indications
- ▶ Monitoring
 - ▶ PHQ-9
 - ▶ Higher number/worse depression
 - ▶ Not perfect

SSRIs

- ▶ Mechanism of Action: By inhibiting serotonin reuptake, it increases serotonin in the synapse and helps improve mood/depression
- ▶ Sertraline (Zoloft), citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), paroxetine (Paxil), fluvoxamine (Luvox)

SSRI Adverse Effects

- ▶ Nausea, diarrhea, GI upset
- ▶ Insomnia or somnolence
- ▶ Sexual dysfunction (↓ libido, anorgasmia, delayed ejaculation)
- ▶ Weight gain (long-term; agent dependent)
- ▶ Hyponatremia / SIADH (higher risk in older adults)
- ▶ QT prolongation (notably citalopram, escitalopram at higher doses)
- ▶ Serotonin syndrome (with other serotonergic drugs)
- ▶ Discontinuation syndrome if abruptly stopped (dizziness, “brain zaps,” flu-like symptoms)
- ▶ Increased bleeding risk (platelet inhibition, ↑ with NSAIDs/anticoagulants)

SSRI Clinical Pearls

- ▶ Citalopram
 - ▶ QTc prolongation, limit dose in elderly to 20 mg daily; omeprazole interaction
- ▶ Fluvoxamine
 - ▶ Generally avoid, multiple 3A4 drug interactions
- ▶ Fluoxetine
 - ▶ A little more activating
- ▶ Sertraline
 - ▶ Loose stools/serotonergic
- ▶ Paroxetine
 - ▶ Generally avoid in elderly, mildly anticholinergic
 - ▶ 2D6 interactions
 - ▶ Tends to be more sedating/weight gain
- ▶ Controversial effect on platelets and bleeding

Common SNRIs

- ▶ Mechanism of Action: Inhibits both serotonin and norepinephrine reuptake
- ▶ Venlafaxine (Effexor), duloxetine (Cymbalta), desvenlafaxine (Pristiq), levomilnacipran (Fetzima), milnacipran (Savella)
- ▶ Often used if corresponding pain syndromes (i.e. neuropathy, fibromyalgia)

Miscellaneous Serotonin Agents

- ▶ Trazodone (Desyrel), nefazodone (Serzone)
 - ▶ Mechanism of Action: 5-HT₂ (serotonin) antagonist and also a weak serotonin reuptake inhibitor, possibly mild antihistamine type effect, not totally understood
 - ▶ Nefazodone rarely used due to hepatotoxicity
 - ▶ Trazodone more often used for its sedative (antihistamine) properties at low doses
 - ▶ 12.5 – 100mg at night
 - ▶ Antidepressant target doses for trazodone are usually higher
 - ▶ Dry mouth, sedation, orthostasis risk
- ▶ Vilazodone (Viibryd), vortioxetine (Trintellix)
 - ▶ GI adverse effects are most common

Mirtazapine

- ▶ Mechanism of Action: Central alpha2 antagonist which increases norepinephrine and serotonin; also blocks histamine receptors (sedative effect) and may antagonize 5-HT2 and 5-HT3
- ▶ Sedating (can help with insomnia, particularly at lower doses)
- ▶ Weight gain – can help with frail elderly with depression
 - ▶ Can be a negative in already overweight patients or for younger patients who don't want to gain weight
- ▶ Option for patients looking to minimize risk of sexual dysfunction side effect

Bupropion

- ▶ Mechanism of Action: Acts by inhibiting dopamine and norepinephrine reuptake (avoids serotonin impact)
- ▶ Activating
- ▶ Increases the risk of seizures (avoid use in patients with seizure history, alcohol abuse, and eating disorder history)
- ▶ Can be used for smoking cessation, ADHD
- ▶ Option for patients looking to avoid sexual dysfunction adverse effect
- ▶ CYP2D6 inhibition

TCA's – lots of them!

- ▶ Mechanism of Action: Inhibition of serotonin and norepinephrine reuptake; highly anticholinergic
- ▶ Nortriptyline (Pamelor), amitriptyline (Elavil), Desipramine (Norpramin), imipramine (Tofranil), doxepin (Sinequan)
- ▶ Risk in overdose
- ▶ Nortriptyline – possibly better tolerated in elderly
- ▶ QTc prolongation
- ▶ Good for corresponding pain syndrome
 - ▶ Fibromyalgia
 - ▶ Neuropathy

MAOIs

- ▶ Isocarboxazid (Marplan), Phenelzine (Nardil), Selegiline (Emsam), Tranylcypromine (Parnate)
- ▶ Mechanism of Action: By inhibiting monoamine oxidase, this ultimately increases norepinephrine, serotonin, and dopamine
- ▶ Last line agent due to drug interactions and tyramine interaction
- ▶ MAOI/Tyramine interaction
 - ▶ Foods high in tyramine: fermented, cured, aged foods such as cheese, smoked meats/fish, beer
 - ▶ Reaction: High BP, tachycardia, N/V, severe headache
- ▶ Multiple contraindicated drug interactions due to risk of serotonin syndrome (i.e. Triptans, SSRIs, linezolid)



Schizophrenia

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Positive Symptoms

- ▶ Hallucinations
 - ▶ Visual
 - ▶ Auditory
- ▶ Delusions
 - ▶ Fixed, false belief
- ▶ Disorganized speech and thoughts

Negative Symptoms

- ▶ Flat affect
- ▶ Lack of interest in things previously enjoyable
- ▶ Trouble functioning in daily life
- ▶ Withdrawn, social isolation

Antipsychotics – Dopamine Antagonists

- ▶ 2nd Generation Antipsychotics: Aripiprazole (Abilify), asenapine (Saphris), cariprazine (Vraylar), clozapine (Clozaril, Fazaclo), lurasidone (Latuda), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon), paliperidone (Invega), iloperidone (Fanapt)
- ▶ 1st Generation Antipsychotics: Haloperidol (Haldol), thiothixene (Navane), fluphenazine (Prolixin), Thioridazine (Mellaril)
- ▶ Mechanism of Action: Binds to Dopamine 2 and 5HT_{2A} (serotonin) receptors which helps regulate the activity of dopamine in the mesolimbic pathway

Selection of Antipsychotic

- ▶ Based upon patient preference
- ▶ Adverse effect profile
- ▶ Previous trials
- ▶ Drug interactions
- ▶ Dosage forms
 - ▶ Adherence

Side Effect Profile, Clinical Considerations

- ▶ Sedation
- ▶ Weight Gain
- ▶ EPS
- ▶ Prolactin
- ▶ Anticholinergic
- ▶ Agranulocytosis
- ▶ QTC prolongation

Best efficacy

- ▶ Clozapine
 - ▶ Not used first line due to agranulocytosis and other risks
 - ▶ Reserved for refractory patients
- ▶ 5 boxed warnings
 - ▶ Neutropenia
 - ▶ Low BP, pulse, syncope
 - ▶ Seizure
 - ▶ Cardiomyopathy
 - ▶ Increased mortality when used in dementia-related psychosis (class warning)

Clinical Pearls

- ▶ Rarely are first generation antipsychotics (i.e. haloperidol) used due to very high rates of extra pyramidal side effects
- ▶ Extra pyramidal symptoms (EPS)
 - ▶ High risk: first generation agents like haloperidol, 2nd generation agents like risperidone, paliperidone and lurasidone
 - ▶ Low risk: quetiapine, clozapine, pimavanserin (only approved for Parkinson disease psychosis)

Clinical Pearls

- ▶ Metabolic syndrome
 - ▶ High risk: olanzapine, clozapine
 - ▶ Low risk: aripiprazole, lurasidone, ziprasidone
- ▶ Hyperprolactinemia
 - ▶ High risk: risperidone, paliperidone
 - ▶ Low risk: aripiprazole, lurasidone

Clinical Pearls

- ▶ QTc prolongation
 - ▶ High risk: ziprasidone, typicals
- ▶ Sedation
 - ▶ High risk: quetiapine, clozapine

Clinical Pearls

- ▶ Periodically monitor for metabolic syndrome in patients on any antipsychotic (lipids, A1C etc.)
- ▶ Long acting injectables are an option for many of the antipsychotics
 - ▶ Make sure oral test doses are done
- ▶ Aripiprazole often used for antidepressant augmentation
- ▶ To help with movement adverse effects (EPS) and also possibly with drooling, you may see anticholinergics used; i.e. benztropine, trihexyphenidyl or diphenhydramine

Long Acting Injectables

- ▶ Aripiprazole – establish tolerability with oral aripiprazole, then give injection once monthly (400 mg) – overlap oral antipsychotic for 14 days
- ▶ Risperidone – establish tolerability with oral risperidone then give injection (25 mg every 2 weeks) and overlap for 3 weeks with oral
- ▶ Paliperidone – test oral tolerability with paliperidone or risperidone; 234 mg injection (oral overlap is not necessary once monthly IM paliperidone is given)
- ▶ Haloperidol decanoate – establish oral tolerability, then give 10-20 times the oral dose (max 100 mg for first injection and the remainder 3-7 days later); taper off oral by approximately 25% per week and may adjust based upon clinical assessment of response
 - ▶ Given every 4 weeks for maintenance

Neuroleptic Malignant Syndrome (NMS)

- ▶ Due to antipsychotic use
 - ▶ Usually happens when initiated or dose is increased
- ▶ Extremely rare
- ▶ Symptoms
 - ▶ High blood pressure
 - ▶ Tachycardia
 - ▶ Very high fever
 - ▶ CNS changes – agitation etc.
 - ▶ Muscle rigidity
 - ▶ Tremor

Neuroleptic Malignant Syndrome (NMS)

- ▶ DC medication
- ▶ Primarily supportive care
 - ▶ Cooling blankets
 - ▶ Cooled IV fluids
 - ▶ Antipyretics
- ▶ Dantrolene
 - ▶ Skeletal muscle relaxant
 - ▶ Can help bring down temperature
 - ▶ Possibly help with rigidity
 - ▶ Risk of liver toxicity
- ▶ Bromocriptine
- ▶ Benzodiazepines