# 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/combativeness 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 $M_1$ 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 $\alpha_2$-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

- Fidgits
- 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), dexmethylphenidate (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

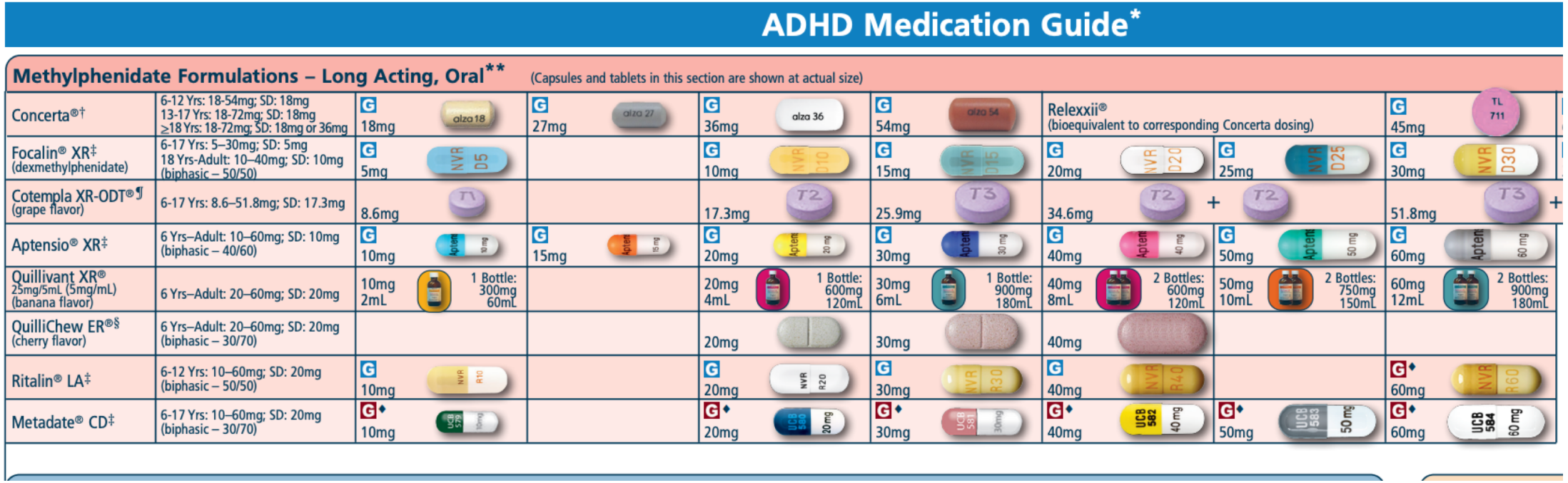
- Bupropion
  - Avoid in seizure disorder
  - Non-controlled
  - Takes a while to work
- Clonidine, guanfacine
  - Antihypertensive effect
    - Rebound hypertension
  - Non-controlled
  - Immediate benefit not likely
  - Fatigue
- Drug holidays are not appropriate with these agents

# 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/



# 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-HT1A 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 5HT2A (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