• Depression Treatments
• Opioids
• Drugs of Abuse
• Sulfa and PCN allergies
Disclaimer

- Off-label, and some dangerous uses of substances discussed.
Depression Treatments
• Depression is 11th cause of mortality worldwide (W.H.O)

• Risk factors of increased incidence:
  • Middle-aged
  • Divorced/Never married
  • Family h/o depression
  • Low (very high) income
  • Unemployed/disabled
  • More than 1 chronic disease
  • Female
Examples of substances associated with Depressive Symptoms

<table>
<thead>
<tr>
<th>Substance</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>alcohol</td>
<td>beta-blockers</td>
</tr>
<tr>
<td>stimulant withdrawal</td>
<td>interferons</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>cholinesterase inhib.</td>
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<tr>
<td>Cimetidine</td>
<td>many anticonvulsants</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Opioids</td>
</tr>
<tr>
<td>heavy metal poisoning</td>
<td>Dopamine agonist (haldol, metoclopramide)</td>
</tr>
</tbody>
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Treatment Options

- Psychotherapy
  - Cognitive behavioral therapy
  - Interpersonal psychotherapy
  - Relapse rates lower than with pharmacotherapy
- Pharmacotherapy
  - Best outcomes when both done in conjunction.
Pharmacotherapy

- Third most common class of meds prescribed (behind cholesterol meds and analgesics).
- 1/3 of pts. taking antidepressants will not have symptom improvement, and >1/2 won’t achieve remission.
- Trials show 1/3 of placebo arms achieve remission.
Pharmacotherapy

- Studies may show statistical significance - but general consensus is that these differences are not **clinically significant**.
- Choose agent based on:
  - previous responses,
  - side effects,
  - DDI,
  - co-morbid conditions,
  - ease of use,
  - cost
Mechanisms of Antidepressants

- Mainly work on 3 neurotransmitters/chemicals in the brain:
  - **Serotonin** *(many classes of subreceptors)*
  - **Dopamine** *(mult. subreceptors)*
  - **Norepinephrine** *(mult. subreceptors)*
Classes of agents (multiple ways of classification)

- SSRI (selective serotonin reuptake inhib.)
- SNRI (serotonin-norepinephrine reuptake inhib.)
- Dopamine (mild norepinephrine) reuptake inhib.
- Alpha2-adrenergic antagonist
- SSRI/Serotonin (5-HT) receptor partial agonist
- SSRI/Serotonin receptor partial agonist/antagonist.
- SSRI/Serotonin subclass antagonist
- Serotonin reuptake inhib/NE; Histamine, Muscarenic, Alpha-Adrenergic Antagonists
- Monoamine Oxidase Inhibitors (MAOIs)
• American Psychiatric Association first line/initial antidepressant treatment options:
  • SSRIs
  • SNRIs
  • Mirtazapine
  • Bupropion
  • ?Vilazodine/Vortioxetine

• Second line/Reserve treatment options:
  • Tricyclics
  • MAOIs
  • Trazadone (given > once a day for depression)
SSRI

• Citolapram (Celexa)
• Escitalopram (Lexapro)
• Fluoxetine (Prozac)
• Fluvoxamine (Luvox)
• Paroxetine (Paxil)
• Sertraline (Zoloft)
SSRI

• Work by inhibiting reuptake of Serotonin at the presynaptic neuron.
• Sertraline, Citolapram, Escitolapram, Fluoxetine, Paroxetine - generic, and many times first tier insurance/$4 formulary.
• Paroxetine not good for obese patient, pregnancy, elderly (sedation); and shouldn’t d/c abruptly.
• Citolapram causes Q-T prolongation (with other meds)
• Side effects shared as a group:
  • Sexual dysfunction
  • Insomnia/sedation
  • Wt. gain
SSRI-like

- Vilazodone (Viibryd)
  - SSRI and partial agonist of 5HT1a receptor (similar to Buspirone)
  - Not shown to be superior to (or as good as in some cases) SSRIs outcomes
  - GI side effects higher than SSRIs (given in starter kit with increasing doses to minimize)
  - More expensive
SSRI-like

- Vortioxetine (Brintellix)
  - SSRI and 5HT1a agonist/5HT3 antagonist.
  - Superior to placebo, but not much comparison to other antidepressants yet.
  - Despite weak antagonism of 5HT3, nausea a problem initially; constipation.
  - More expensive
SNRI

- Venlafaxine (Effexor)
- Desvenlafaxine (Pristiq)
- Duloxetine (Cymbalta)
- Levomilnacipran (Fetzima)
SNRI

- Serotonin and Norepinephrine reuptake inhibitor (to lesser extent, dopamine)
- Monitor blood pressure
- Maybe good for psychomotor slowing or chronic pain.
- Maybe not good for uncontrolled HTN, agitation, or insomnia.
- May have significant rebound side effects if stopped abruptly.
- Levomilnacipran stronger NE at higher doses (doesn’t mean better outcomes). Active isomer of Milnacipran (indicated for Fibromyalgia).
Bupropion

- Dopamine (mild norepinephrine) reuptake inhibitor.
- Only one in its class currently (Wellbutrin, Aplenzin)
- Multiple salts and non-AB rated generics are confusing.
- Good if sexual dysfunction a concern
- May help quit smoking (Zyban)
- May be good in pts. with fatigue/somnolence
- May help lose wt.
- *Not* good in uncontrolled HTN, agitation, insomnia
- Theoretically can raise seizure threshold
- Can combine with other, more Serotonergic meds (SSRIs)
Mirtazapine

- Alpha-2 adrenergic antagonistic (which results in increased release of NE and Serotonin), antagonist of 5-HT2/5HT3/Histamine receptors. Moderate peripheral Alpha-1 adrenergic and muscarinic antagonist.
- Only one in it’s class (Remeron)
- May have faster onset, but no difference in effectiveness at 4 weeks.
- Significant for wt. gain and sedation (good for insomnia/agitation, but not obesity)
- No significant CYP450 DDI
- Sexual dysfunction usually not a concern
Trazodone

- Antagonist of 5-HT2a and 5-HT2c, with weaker SSRI properties. Also a Histamine and Alpha-1 adrenergic antagonist.
- Due to antagonism of 5-HT2a/Histamine antagonist, has side effect of significant sedation - therefore used many times to help insomnia caused by SSRIs (lower doses).
- Also, due to 5-HT2a antagonism, can help with sexual dysfunction of SSRIs.
- 5-HT2c antagonism - may cause wt. gain (opposite of Lorcaserin)
- Can be used as an augmentation of SSRIs.
Tricyclics

- Usually 2nd or 3rd line antidepressants.
- May work better in severe depression cases.
- Block reuptake of 5-HT, Norephinephrenine, antagonists of Histamine, muscarenic, and alpha-adrenergic receptors.
- Amitriptyline and Imipramine most arrhythmogenic.
- Nortriptyline and Desipramine are least anticholinergic.
Optimizing Therapy

• Response vs. Remission
  
  • Response = 50% reduction in symptoms.
  
  • Remission = almost complete absence of symptoms (only happens ~ 1/3 of the time). Goal should be remission.
Optimizing Therapy

- Adherence, expectations:
  - Can see an effect in 2 weeks
  - At least 8 weeks (at an effective dose) before considering a change
  - At least 12 weeks (at effective dose) before labeling it a treatment failure.
  - Pts. often get stuck on a starting dose without being titrated up.
  - Only 50% of pts. are still on therapy after 2 months
  - 6 months is a reasonable minimal goal of therapy.
Optimizing Therapy

- Most should not be stopped abruptly - pt. may experience discontinuation syndrome:
  - Dizzy
  - Irritable
  - Nausea
  - Fatigue
  - Muscle aches
  - “Electric shocks”
- Usually best to taper off over 2 - 4 weeks
  - Tapering also may decrease depression relapse
Optimizing Therapy

• Side effects usually biggest obstacle to continuation.
  • Sexual dysfunction:
  • Add/switch to Bupropion or Mirtazepine
  • Add Trazadone (small risk of priapism)
  • Paroxetine has highest risk.
  • Stimulants (Methylphenidate)
  • Decreased dose of antidepressant
  • Addition of Phosphodiesterase Inhibitor (Sildenafil, Tadalafil, etc.)
Optimizing Therapy

- Side effects (cont’d)
  - **GI:**
    - Fluoxetine has highest rates of N/V among SSRIs.
    - Sertraline - more likely for diarrhea
    - Vortioxetine - 1/3 of pts. N/V.
    - SNRIs - high rate of N/V (Venlafaxine, Duloxetine)
    - Vilazodone - should be titrated up over 2 weeks to minimize N/V/D/abd. cramping.
Optimizing Therapy

- Side effects (cont’d)
  - Weight gain:
  - May be beneficial if underlying depression causing wt. loss.
  - Mirtazepine - well-recognized side effect.
  - Bupropion switch/addition can decrease wt. gain; maybe wt. loss.
Optimizing Therapy

- Side effects (cont’d)
  - **Insomnia/somnolence:**
  - SSRI/SNRIs - insomnia common.
  - Don’t take Fluoxetine, Sertraline, or Bupropion close to bedtime.
  - Small dose of Trazodone ~1 hr. prior to bedtime can help.
  - Mirtazepine can cause sedation - take qhs.
  - Non-Benzodiazepines for short course, to help get over the initial few weeks.
Optimizing Therapy

• Switching/combining antidepressants
  • Agents that have shown some evidence for switching to:
    • Sertraline
    • Escitolapram
    • Duloxetine
    • Venlafaxine
    • Mirtazapine
    • Bupropion
Optimizing Therapy

• Switching/combining antidepressants
  • Most often used combinations:
    • **Bupropion** added to SSRI/SNRI - may not be good for those with high levels of anxiety
    • **Mirtazepine** added to SSRI/SNRI - may be good for insomnia, reduce nausea, improve appetite
    • **Trazadone** added to SSRI/SNRI - may help with insomnia
Optimizing Therapy

• Drug-drug interactions
  • Not only when starting antidepressant, but also when stopped, or other medication added.
  • Side effect from antidepressant that subsided early in treatment may resurface if DDI with starting/stopping another medication.
• Not insignificant
Optimizing Therapy

- **Augmentation of antidepressants**
  - Non-antidepressant meds generally used if adequate doses of antidepressants may achieve a response, but not remission.
  - **Low dose** atypical antipsychotics
    - Aripiprazole and Quetiapine have best evidence to date
    - Eg: 1 - 5mg of Aripiprazole
    - Eg: Fluoxetine/Olanzapine is approved combo. med for treatment-resistant depression
    - Maybe help with SSRI side effect of sexual dysfunction/insomnia
    - Main drawback is antipsychotic metabolic side effects
    - Wt. gain, hyperglycemia, hyperlipidemia
Opioids & Drugs of Abuse
Newer Formulations

- Rapid increase in new opioid derivatives and formulations over last several years.
- **Xartemis XR** - BID extended-release Oxycodone/Acetaminophen (7.5/325 - i-ii po BID), part of dose released immediately and the rest is released gradually.
- **Zohydro ER** - first single ingredient, extended-release form of Hydrocodone
  - BID formulation
  - Significant controversy over its approval
  - *NOT* a tamper-resistant formula - can be crushed so all of drug released at once
  - Taken with EtoH can speed up absorption and almost **double** Hydrocodone levels.
- **Evzio** - 1st Naloxone *auto*-injector for opioid overdose (like Epipen)
Change in Schedule

- Hydrocodone combination meds will become scheduled CII in early October.
- Hydrocodone combination products (HCP) - discontinued all combos with >325mg Acetaminophen now.
  - Reformulated Vicodin HP will have 300mg of Acetaminophen.
- Acteaminophen with codeine and Tramadol only opioid that’s not CII.
- Tramadol is now CIV on federal level (thought to have same abuse potential as Propoxyphene)
Drugs of Abuse

- Drug-deterrent formulations *not* required by the FDA.
- Being promoted to decrease abuse, but not been proven - could cause abusers to move to other opioids, or heroin.
- Can cost *much* more than traditional products
- Opioid-antagonist formulations - contain Naloxone to block some of the high if the tab/cap is crushed, then snorted/injected.
- Tamper-resistant products - (eg: Oxycontin, Exalgo) - break into clumps if crushed, or turns into a thick gel if liquid added, so can’t be snorted/injected.
Drugs of Abuse

• “Bath Salts”
  • Designer potent synthetic stimulants - derivative of substance in Khat plant (E. Africa, S. Arabia) - sold in head/smoke shops, convenience store, gas stations
  • Sold as: Cloud 9, Ivory Wave, Vanilla Sky, Blue Silk, M-CAT, and marketed as bath crystals, plant food - not subject to regulations
  • Causes euphoria, increased sociability and libido, but also agitation, paranoia, hallucinatory delirium.
  • Plant is not illegal, but Cathinone ingredient is.
  • Does not show up on routine drug tests.
Drugs of Abuse

• **Antihistamines**
  • Benedryl, Dramamine, Phenergan, etc.
  • Causes increased euphoria with opioids, decreases insomnia/anxiety form opioid withdrawl, hallucinations.
Drugs of Abuse

- Clonidine
  - Prolongs effects of Benzos, cocaine, opioids; reduces withdrawal symptoms of opioids/alcohol
  - Health consequences: hypotension and withdrawal symptoms upon discontinuation.
Drugs of Abuse

• Synthetic Marijuana
  • Wide variety of herbal mixtures that produce Cannabis-like effects
  • “Spice” (K2, skunk, etc.) marketed as “natural substances”, but analysis shows active ingredients are synthetic cannabinoids.
  • 5 active ingredients are C-I by DEA, making it illegal. Manufactures substitute different chemicals - sold in head shops/gas stations
  • Popular with high schoolers - second most commonly used illicit substance, after Marijuana
  • Chemicals act at Cannabinoid receptor, but some have higher affinity, and therefore can produce different, or more unpredictable effects than marijuana.
Drugs of Abuse

- Gamma hydroxybutyrate (GHB)
  - **Xyrem** - CNS depressant approved by FDA in 2002 for tx. in Narcolepsy, and is a metabolite of GABA.
  - “Grievous bodily harm, liquid x, Goop, easy lay”.
  - Reduces pain/anxiety, feelings of well-being, lowered inhibitions, poor concentration and impaired memory and judgement, decreased blood pressure, loss of some reflexes
  - No reliable GHB detection tests.
Drugs of Abuse

• **Ketamine**
  • Dissociative anesthetic, mostly used in veterinary practice.
  • Distorts perceptions of sight and sound; produces feelings of detachment from environment
  • Effects at a type of Glutamate receptor (NMDA)
  • “Cat Valium, Special K, Kit Kat”
Drugs of Abuse

- **Salvia**
  - Herb in *mint* family, native to S. Mexico.
  - “Shepherdess’ Herb, Maria Pastora, Magic mint, Sally-D”
  - Dissociative/modified sense of reality and self; emotional swings
Drugs of Abuse

- Relaxation Drinks
- Anti “Energy - drinks”
  - “Neuro Bliss, Just Chill, Marley’s Mellow Mood”
  - Contain supplements promoted for their calming/sedating effects: Valerian, Kava-kava, GABA, melatonin, etc.
  - Amounts of ingredients many times not listed
  - Valerian and Kava-kava OTC supplements linked with **fulminant hepatic failure**.
- Not regulated by FDA
Drugs of Abuse

- **Electronic cigarettes**
  - “N-Joy, Blu, e-Cig” - “Vaping” Liquid nicotine cartridges with battery powered atomizer that heats/vaporizes in order to be inhaled/exhaled.
  - Government surveys show many high schoolers using e-cigs. that have not smoked in the past - no age restrictions to buy. Certainly addictive potential (comes in candy flavors)- Cigarette companies have bought e-cig. companies.
  - Not regulated currently (b/c don’t contain leaf tobacco), but FDA proposing regulation.
  - Each cartridge ~ 1 pack cigarettes in nicotine equivalents (most cost about the same as pack of cigarettes). Nicotine may not be uniform concentration in cartridge
  - Quality safety studies not done - concern over strengths, impurities, and second-hand exposure of vapor.
Drugs of Abuse

- drugabuse.gov/drugs-abuse
- livertox.nih.gov
Urine Drug Testing

- Limitations: initial testing is usually with immunoassay, which are subject to false positives. Labs most times will automatically send for confirmation with liquid/gas chromatography with mass spectrometry.

- Immunoassays vary in specificity
  - Opioid assay may either not detect, or unreliably detect synthetic (Fentanyl, Methadone), or semi-synthetic (Oxycodone) opioids
Urine Drug Testing

- Negative results may suggest:
  - intermittent use
  - running out of medication early/prn use
  - diversion
- Lack of detected metabolites suggests:
  - acute ingestion
  - Genetic variations/drug interactions that impair metabolism
  - Addition of the drug directly into the urine sample
- Urine samples can be checked for temperature (90-100 degrees), if within four minutes after collection, to catch those bringing in “clean urine”
Urine Drug Testing

- **Amphetamines: False positives**
  - amantadine
  - brompheniramine
  - bupropion
  - chlorpromazine
  - labetalol
  - promethazine
  - ranitidine
  - trazadone
Urine Drug Testing

• Benzodiazepines:
  • Detected up to 3 days (shorter-acting - Lorazepam); up to 30 days in long-acting - Diazepam, chlordiazepoxide.
  • Sertraline can cause a false positive.
  • Some immunoassays do not reliably detect Lorazepam or Clonazepam (mass spectrometry preferred).
Urine Drug Testing

- **Cocaine:**
  - Detected 1-4 days after last dosing
  - No known false positives

- **Marijuana:**
  - Can detect: 3-7 days (single use); 5-7 days (moderate use); 10-15 days (daily use); > one month (long term, heavy use).
  - Dronabinol (synthetic THC) can test +
  - Passive inhalation, or ingestion of hemp-containing foods unlikely to cause a positive
Sulfa Allergies
Sulfa Allergies

• Many times confusion about which drugs are *Sulfonamides* (SO$_2$NH$_2$), and how likely are they to cross-react (cross-sensitivity)

• 3 classes of Sulfonamides:
  • Sulfonylarylamines
  • Non-sulfonylarylamines
  • Sulfonamide moiety-containing meds
Sulfa Allergies

- About 3% of population have true allergy to sulfa antibiotics - most commonly manifested as maculopapular rash.
- Sulfates, Sulfur, Sulfites, and Sulfones (Dapsone) are chemically unrelated to Sulfonamides and generally do not cross-react.
Sulfa Allergies

• Degree of allergy reaction is one of the most important things to keep in mind.

• Any significant organ involvement or Steven-Johnson syndrome as a reaction should not be tried on a med in a related class.
Sulfonylarylamines

- Most likely to cause a sulfa allergy; cross sensitivity is possible - even with topicals/ophthalmics
- Sulfa Abx: TMP/SMX, Sulfadiazine, Sulfacetamide
- Sulfasalazine: metabolized to Sulfapyridine and 5-aminosalicylic acid; Sulfapyridine is a Sulfonylarylamine that is systemically absorbed
- Darunavir and Fosamprenavir (precaution)
Nonsulfonylarylalamines

• Have structures that are *similar* to Sulfonylarylalamines - but are different enough that cross-sensitivity is rare.
  • Celecoxib
  • Loop diuretics: Bumetanide, Furosemide, Torsemide
  • Sufonylureas: Chlorpropamide, Glimeperide, Glipizide, Glyburide
  • Thiazides: HCTZ, Chlorthalidone, Indapamide, Metolazone
  • Carbonic Anhydrase Inhibitors: Acetazolamide, Dorzolamide
Sulfonamide Moiety

- Have a sulfonamide group, but the total chemical structure is usually quite different.
- Sumatriptan, Naratriptan, Sotolol, Topiramate, Simeprevir
You're a pain in my ass. Stop being that.