Pharmacology & Pharmacotherapy

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- Depression Treatments
- Opioids
- Drugs of Abuse
- Sulfa and PCN allergies

Disclaimer

- Off-label, and some dangerous uses of substances discussed.

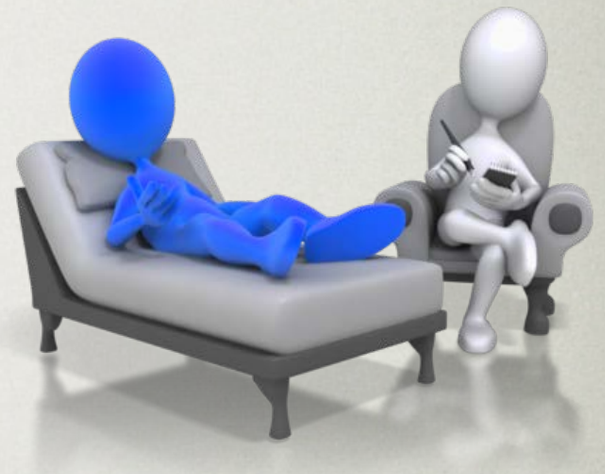
Depression Treatments

- 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

alcohol	beta-blockers	sedative hypnotics
stimulant withdrawl	interferons	chemotherapy
Tamoxifen	cholinesterase inhib.	Isotretinioin
Cimetidine	many anticonvulsants	Clonidine
Methyldopa	Opioids	Varenicline (Chantix)
heavy metal poisoning	Dopamine agonist (haldol, metoclopramide)	Efavirenz (Sustiva)

Treatment Options



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

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)

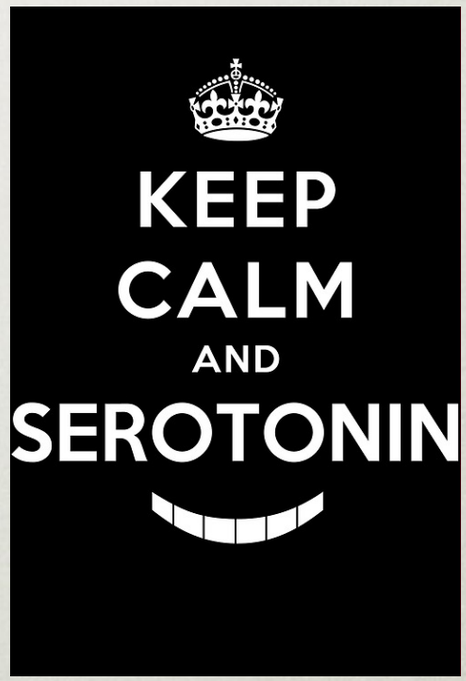
Classes of agents
(multiple ways of classification)

- 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 it’s 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 Imiparamine most arrhythmic.
- Nortriptyline and Desipramine are *least* anti-cholinergic

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

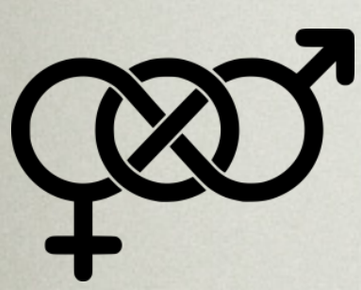
- Adherence, expectations:
  - Can see an effect in 2 weeks
  - At least 8 weeks (at an effective dose) before considering a change
  - At least 12 weeks (at effective dose) before labeling it a treatment failure.
  - Pts. often get stuck on a starting dose without being titrated up.
  - Only 50% of 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.
  - <u>Sexual dysfunction</u>:



  - 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)
  - <u>GI</u>:
    - 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)
  - <u>Weight gain</u>:
    - 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
    - Mirtazepine
    - 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 antidepression 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 derivitives 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 it's 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 opiods, decreases insomnia/anxiety form opioid withdrawl, hallucinations.

Drugs of Abuse

- Clonidine
  - Prolongs effects of Benzos, cocaine, opioids; reduces withdrawl symptoms of opioids/alcohol
  - Health consequences: hypotension and withdrawl 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

- <u>Salvia</u>
  - 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

- <u>Relaxation Drinks</u>
  - 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 *<u>fulminant hepatic failure</u>*.

  - Not regulated by FDA

Drugs of Abuse

- <u>Electronic cigarettes</u>
  - “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 - <u>*no*</u> 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_2NH_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)

Nonsulfonylarylamines

- Have structures that are *similar* to Sulfonylarylamines - 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.

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