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Antidepressant Medications

Selective Serotonin Re-uptake Inhibitors (SSRI's)

Fluoxetine (Prozac), Sertraline (Zoloft), Paroxetine (Paxil), Citalopram (Celexa), Escitalopram (Lexapro)

1. Uses:
   Mood disorders: Major Depression, Persistent Depressive Disorder (Dysthymia),
   Premenstrual Dysphoric Disorder (PMDD)
   Anxiety disorders: GAD, Panic Disorder, Social Anxiety Disorder
   Eating disorders: Bulimia Nervosa, Binge Eating Disorder
   Other disorders: Post Traumatic Stress Disorder (PTSD), Obsessive Compulsive Disorder (OCD),
   Body Dysmorphic Disorder, Somatoform Disorders

2. General side effect profile
   Generally benign.
   None of the SSRI's significantly effect alpha-adrenergic, histaminic, or cholinergic receptors with the exception of paroxetine (paxil) which is weakly anti-cholinergic
   Side effects from SSRI's are attributed to their effects upon serotonin receptors

3. What should a clinician educate a patient about when prescribing an SSRI?
   SSRI's tend to have similar side effects profiles; However, certain SSRI's may be more likely to cause specific side effects so some patients who cannot tolerate one SSRI may do well on another

   Issues to be discussed include: side effects, time to response, drug interactions, and stopping the medication
   - **Common side effects**:
     - **Sexual dysfunction** (most common)
     - Drowsiness, insomnia, **anxiety**, dizziness, headache, **GI symptoms**
     - **Weight gain**
       - Effect depends upon the specific medication and the length of treatment
       - **Short term treatment for two to three months with SSRI's usually causes little or no weight change. Longer term treatment may result in weight gain**. However, in some cases it is not clear if this is a true medication side effect or the result of recovery from depression and the reversal of undesired weight loss
       - Studies suggest paroxetine (Paxil) may be the most problematic of the SSRI's
   - Uncommon side effects
     - Suicide risk: This is a controversial topic within the field of psychiatry
       There is no clear evidence that treating depressed patients with SSRI's, or antidepressants in general, increases or decreases the risk of suicidality (suicidal ideation, preparatory act, attempts, or death). There may be an age specific effect of anti-depressants upon suicidality.
       Antidepressants may raise the risk of suicidality in patients age 18-24, have no effect upon patients age 25-30, and may lower the risk in patients 31 years and older.
       Also, it is important to note the connection between untreated depression the increased risk of suicidality.
     - Overdose on a single SSRI alone rarely causes death or serious sequelae. Overdoses of up to 30 times the usual daily dose (1 month of a prescription) typically produce minor or no symptoms
     - Cardiac side effects
       - Citalopram (Celexa) causes dose dependent QT interval prolongation which may lead to a life threatening arrhythmia. As such, there is a recommended maximum dose (40mg).

4. Time to response: **Full therapeutic effects** of SSRI's may not appear for **3-8 weeks**

5. Drug-drug interactions
   Some SSRI's are moderate to potent inhibitors of cytochrome P450 drug metabolism and can lead to drug-drug interactions by altering blood levels of other medicine that depend on these enzymes for clearance or activation.
   - Citalopram (Celexa) and escitalopram (Lexapro): cause the least inhibition and are the SSRI's of choice for situations in which drug-drug interactions are a concern.
   - Sertraline (Zoloft) is a reasonable alternative.

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Serotonin Syndrome

- Seen with therapeutic medication use, inadvertent interactions between drugs, and intentional self-poisoning; most typically the cause is an interaction between multiple medications
- Majority of cases **present within 24 hours, most within 6 hours, of a change or initiation of a drug**
- Diagnosis
  - Made solely on clinical grounds; no labs tests confirm diagnosis
  - Hunter criteria: patient took a serotonergic agent and meets one of the following conditions
    - Spontaneous clonus
    - Inducible clonus plus agitation or diaphoresis
    - Ocular clonus plus agitation or diaphoresis
    - Tremor plus hyperreflexia
    - Hypertonia plus temp > 38°C (100.4°F) plus ocular clonus or inducible clonus
- Treatment
  - Discontinue all serotonergic agents
  - Supportive care aimed at normalization of vital signs
  - Sedation with a benzodiazepine
  - Administration of serotonin antagonists: cyproheptadine (Periactin)
- Course
  - Serotonin syndrome **often resolves within 24 hours of discontinuing the serotonergic agent**; however drugs with long half-lives or active metabolites may cause symptoms to persist
    - MAOI's carry the greatest risk; symptoms can persist for several days
    - Fluoxetine (Prozac)'s half-life is 1 week and the half-life of the primary metabolite is 2.5 weeks

6. Stopping the medication: Discontinuation Syndrome

- Abruptly stopping or rapidly tapering antidepressants often causes adverse effects, sometimes referred to as a "discontinuation syndrome"; has been best characterized involving SSRI's
- Most common symptoms include:
  - Dizziness, fatigue, headache, nausea, anxiety, chills, diaphoresis, dysphoria, insomnia, irritability, myalgia, paresthesia, rhinorrhea, tremor
  - Less common, but more memorable symptom: electric like shocks/zaps
- Course
  - Discontinuation symptoms **typically occur within 1-4 days of abruptly stopping/rapid tapering** Although symptoms are usually mild and dissipate over 1-2 weeks, without treatment distressing symptoms may persist for a month or longer
- Risk factors for discontinuation syndrome
  - Short half-life of drug
  - Higher doses of drug
  - Longer duration of treatment at therapeutic doses
  - Anxiety symptoms at onset of antidepressant treatment
- Likelihood
  - SSRI with least risk: fluoxetine (Prozac)
  - Atypical antidepressant with least risk: bupropion (Wellbutrin)
  - SSRI's with greatest risk: paroxetine (Paxil)
    - Occurs 10x's more with paroxetine (Paxil) than sertraline (Zoloft)
    - Occurs 100x's more with paroxetine (Paxil) than fluoxetine (Prozac)
  - SNRI's Greatest Risk: venlafaxine (Effexor), desvenlafaxine (Pristiq)
- Treatment options
  - Mild symptoms—reassurance
  - Moderate to severe symptoms
    - decrease rate of taper;
    - restart drug at dose before symptoms started and decrease rate of taper;
    - may switch to fluoxetine (Prozac) and then taper
- Preventing Discontinuation Syndrome
  - Taper antidepressant by a fixed amount or fixed percent over at least 2-4 weeks

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- Discontinuation syndrome vs Relapse of Depression
    - Among patients who stop their medication and abruptly relapse, it may be difficult to distinguish a discontinuation syndrome from a relapse of depression as some of the symptoms (dysphoria, fatigue, insomnia) are the same
    - However, timing of the resolution of symptoms may offer some clarification:
        - Resolution of symptoms within a few days of restarting the antidepressant is more consistent with discontinuation syndrome;
        - Resolution of symptoms after 1-2 weeks of watchful waiting (no medication being restarted) is also more consistent with discontinuation syndrome

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Serotonin Norepinephrine Re-uptake Inhibitors (SNRI's)

Venlafaxine (Effexor), Desvenlafaxine (Pristiq), Duloxetine (Cymbalta)

1. Uses:
   Mood disorders**:** Major Depression, Persistent Depressive Disorder (Dysthymia)
   Anxiety disorders: GAD, Panic Disorder, Social Anxiety Disorder
   Chronic Pain syndromes: Diabetic peripheral neuropathy, Fibromyalgia, Chronic musculoskeletal pain
   Other disorders: Post Traumatic Stress Disorder (PTSD), Obsessive Compulsive Disorder (OCD), Body Dysmorphic Disorder

2. General side effect profile
   None of the SNRI's significantly effect alpha-1 adrenergic, histaminic, or dopaminergic receptors. **Side effects from SSRI's are attributed to their effects upon serotonin receptors and norepinephrine receptors**.
   Note: SNRI's do not significantly effect cholinergic receptors but the stimulation of the norepinephrine receptors may cause anti-cholinergic like side effects (constipation, dry mouth, urinary retention).

3. What should a clinician educate a patient about when prescribing an SNRI?

   Issues to be discussed include: side effects, time to response, drug interactions, and stopping the medication
   - Common side effects:
       - **Nausea (most common)**
       - **Sexual dysfunction,** dizziness, sweating, dry mouth, insomnia, constipation, headaches
       - **Weight gain**
           - **Short term treatment for two to three months with SNRI's usually causes little or no weight change. Longer term treatment may result in weight gain.**
   - Uncommon side effects
       - Higher blood pressure
           - Blood pressure can increase and appears to be related to the potency of the norepinephrine effects; frequency of this side effect is low.
           - Note, duloxetine (Cymbalta) does not appear to cause this side effect
       - Suicide risk: This is a controversial topic within the field of psychiatry (see SSRI section)
         .
         Overdose on a single SNRI is uncommon-to-rarely dangerous but is more dangerous than an SSRI
           - Can cause hypertension, hypotension, cardiac arrhythmias, seizures, serotonin syndrome and death

4. Time to response
   While some response may take place within the first 2 weeks, it may take many weeks (8+) for a full response

5. Drug-drug interactions
   Most SNRI's do not have clinically meaningful effects on the P450 drug metabolism system.

6. Stopping the medication-risk of discontinuation syndrome
   - (see SSRI section)
   - SNRI's with Greatest Risk: venlafaxine (Effexor), desvenlafaxine (Pristiq)

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Atypical Antidepressants

Bupropion (Wellbutrin), Mirtazapine (Remeron)

Bupropion (Wellbutrin)

1. Uses
   Mood disorders-Major Depression, Seasonal Affective Disorder
   Attention Deficit Hyperactivity Disorder (ADHD)
   Tobacco Dependence

2. General side effect profile
   - Classified as a dopamine-norepinepherine reuptake inhibitor
   - **Structurally related to amphetamines**
     - Mildly **stimulating**:
       - **Beneficial: depressed patients with fatigue, hypersomnia, or poor concentration**
       - **Detrimental: patients may interpret as anxiety; can cause insomnia**
   - Limited effects on other neurotransmitter systems
     - Does **NOT cause sexual side effects**
     - Does **NOT cause weight gain**: studies suggest Bupropion (Wellbutrin) is weight neutral or may even cause a small amount of weight loss

3. What should a clinician educate a patient about when prescribing Bupropion (Wellbutrin)?

   Issues to be discussed include: side effects, time to response, drug interactions, and stopping the medication
   - Common side effects:
     - Dry mouth, GI symptoms, Insomnia (3 most common)
     - Dizziness, Anxiety, Tremor
   - Uncommon side effects
     - Suicide risk: This is a controversial topic within the field of psychiatry (see SSRI section)

       Overdose on Bupropion (Wellbutrin) may cause seizures, hypertension, tachycardia, arrhythmias, and death

   - **Seizure Risk**
     - Appears to be correlated with dose
     - Especially a concern in patients with Eating Disorders (Bulimia Nervosa or Anorexia Nervosa) and bupropion (Wellbutrin) use is contraindicated in these patients.

4. Time to response
   While some response may take place within the first 2 weeks, it may take many weeks (8+) for a full response

5. Drug-drug interactions
   - Metabolized by cytochrome p450 enzyme 2D6; meds that inhibit this enzyme may raise the concentration of bupropion (Wellbutrin)
6. Stopping the medication-risk of discontinuation syndrome
   - appears to be **no significant risk of withdrawal or discontinuation syndrome** with bupropion (Wellbutrin)

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Mirtazapine (Remeron)

1. Uses
   Major Depression, Generalized Anxiety Disorder (GAD)

2. General side effect profile
   - Classified as a noradrenergic and specific serotonergic antidepressant (Nassa):
     - Antagonizes pre-synaptic alpha-2 adrenergic receptors and
     - Antagonizes postsynaptic serotonin 5-HT2 and 5-HT3 receptors
       - 5-HT2 agonism believed to cause sexual dysfunction; since drug is a 5HT2 antagonist, no sexual dysfunction
   - Has **high affinity for histamine H-1 receptors**
     - Likely cause of **drowsiness/sedative side effects**
     - May contribute to **weight gain side effect**

3. What should a clinician educate a patient about when prescribing Mirtazapine (Remeron)?

   Issues to be discussed include: side effects, time to response, drug interactions, and stopping the medication
   - Common side effects:
     - Dry mouth, Drowsiness/sedation, Increased appetite/weight gain

   - Uncommon side effects
     - Suicide risk: This is a controversial topic within the field of psychiatry (see SSRI section)
       Overdose-while is commonly benign, cardiac arrest and death have rarely been reported
     - Serotonin syndrome-Lack of agreement in literature as to whether mirtazapine (Remeron) may cause serotonin syndrome. At most, appears to be much lower risk compared to other antidepressants such as MAOI's, TCA's, SSRI's/SNRI's

4. Time to response
   While some response may take place within the first 2 weeks, it may take many weeks (8+) for a full response

5. Drug-drug interactions: Generally not a problem

6. Stopping the medication- risk of discontinuation syndrome
   - While abrupt stopping can cause a discontinuation syndrome it is much less common an occurrence than with SSRI's or SNRI's

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Tricyclic Antidepressants (TCA's)

Amitriptyline (Elavil), Imipramine (Tofranil),
Desipramine (Norpromin), Nortriptyline (Pamelor),
Clomipramine (Anafranil), Doxepin (Sinequan)

1. Uses
   Mood disorders-Major Depression
   Anxiety disorders-GAD, Panic Disorder
   Other disorders: Post Traumatic Stress Disorder (PTSD), Obsessive Compulsive Disorder (OCD), Bulimia Nervosa, Chronic Pain Disorders

   TCA's are no longer first line or second line medications due to their side effect profile and safety concerns in overdose situations. Are typically 4th or 5th line options for treatment resistant psychiatric disorders.
2. General Side Effect profile
   - Mechanism of action: serotonin and norepinephrine reuptake inhibitors (SNRI's): sexual side effects common

   - **Anti-alpha adrenergic**: may cause orthostatic hypotension, sweating
   - **Anti-histaminic**: may cause sedation, increased appetite/weight gain,
   - **Anti-muscarinic**: may cause blurred vision, constipation, dry mouth, urinary retention

   Overdose
   - **Dangerous in overdose; Fatal in doses as little as 10x's the daily dose**
   - Risks
     - anti-cholinergic toxicity
     - seizures
     - prolongation of QT interval and arrhythmias

Monoamine Oxidase Inhibitors (MAO-I's)

Phenelzine (Nardil), Tranylcypromine (Parnate), Selegiline (Emsam)

No longer first or second line antidepressant medications due to their side effect profile.
When used is most commonly for treatment resistant depression.

Side effects/Drug-Drug Interactions

Hypertensive Crisis

- sometimes referred to the "cheese reaction"
- can occur after patients on MAOI's ingest foods containing the sympathomimetic tyramine; **tyramine is usually metabolized in the GI tract, but the blockade of GI tract MAO allows tyramine to flow into the general circulation causing increased blood pressure**

Serotonin Syndrome

- episodes that involve an MAOI's may be more severe and often lead to adverse outcomes, including death;
  - Likely the risk of an increased severity is related to **MAOI's mechanism of action in which the intracellular monoamine oxidase enzyme is deactivated**; metabolism and elimination of the MAOI drug is insufficient to fix the situation; new monoamine oxidase enzymes must also be made by the cell

- Classically seen with the administration of 2 or more serotonergic agents (Ex. MAOI & SSRI)
  - May also be seen from the administration of a serotonergic agent or the increase in dose of a serotonergic agent in a patient who is sensitive to serotonin