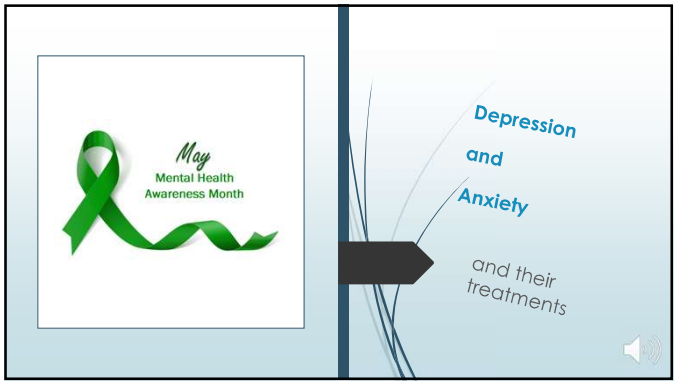
May
Mental Health
Awareness Month
Depression
and
Anxiety
and their
treatments

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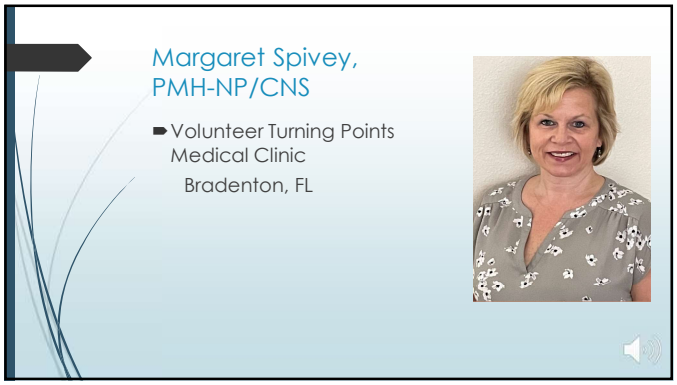
Margaret Spivey,
PMH-NP/CNS
Volunteer Turning Points
Medical Clinic
Bradenton, FL

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Disclosure Statement
I have no affiliation or financial disclosures to any company product or service mentioned in the presentation

3

Objectives

Pathophysiology of anxiety and major depressive disorder

Recognize signs and symptoms of psychiatric disorders in primary care

Identify major classes of psychotropic medications and other treatments

4

Anxiety Disorders

- **Generalized Anxiety Disorder (GAD)**
- **Panic Disorder**
- **Panic Attacks (specifier)**
- **Agoraphobia**
- **Social Anxiety Disorder (SAD)**
- **Specific Phobias**

- **Plus DSM-V**
- **Obsessive Compulsive Disorder-OCD (Obsessive Compulsive and Related Disorders)**
- **Post- Traumatic Stress Disorder- PTSD (Trauma and Stress Related Disorders)**

5

Anxiety Prevalence in U.S. (NAMI, 2017)

- **Anxiety Disorders (plus PTSD and OCD) affect ~ 42 million adults in the U.S.**
- **Approximately 31.1% of U.S. adults experience any anxiety disorder during their lifetime**
- **Female to male ratio is ~ 2:1 across all age groups**
- **60% of those with anxiety will also have symptoms of depression**

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DSM-V Criteria

- Generalized Anxiety Disorder (GAD)
  - ✓ Excessive anxiety and worry about a variety of topics, events, or activities (work/school). Worry is excessive; occurs more often than not for at least **6 months**
  - ✓ Individual finds it difficult to control the worry and it causes significant distress or impairment in social, occupational, or other important areas of functioning.
  - ✓ The anxiety/worry are associated with **3 or more** of the following symptoms:

-Restlessness/feeling keyed up or on edge
-Easily Fatigued
-Difficulty concentrating/mind going blank
-Irritability
-Muscle tension
-Sleep disturbances

Screening Tool GAD-7 (subjective)

7

DSM V Panic Attack

- An abrupt surge of intense fear or intense discomfort that reaches a peak within minutes and during which time ***4 or more*** of the following symptoms occur.

- Palpitations, pounding heart, or accelerated heart rate
- Sweating
- Trembling or shaking
- Sensations of shortness of breath or smothering
- Feeling of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, unsteady, lightheaded, or faint
- Derealization (feelings of unreality) or depersonalization (being detached from oneself)
- Fear of losing control or "going crazy"
- Fear of dying
- Paresthesia (numbness or tingling sensation)
- Chills or hot sensations

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DSM V Panic Disorder Criteria

- Recurrent and unexpected panic attacks (see below)
- ≥1 attack has been followed by 1 month or more of 1 or both of the following
- Persistent concern about additional attacks or their consequences
  A significant maladaptive change in behavior related to the attacks
- The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse or a medication) or a general medical condition
- The panic attacks are not better accounted for by another mental disorder.

9

DSM- V

DSM 5 Criteria
Agoraphobia

A. Marked fear or anxiety about two (or more) of the following five situations:
   1. Using public transportation (e.g., automobiles, buses, trains, ships, planes).
   2. Being in open spaces (e.g., parking lots, marketplaces, bridges).
   3. Being in enclosed places (e.g., shops, theaters, cinemas).
   4. Standing in line or being in a crowd.
   5. Being outside of the home alone.

B. The individual fears or avoids these situations because of thoughts escape might be difficult or help might not be available in the event of developing panic-like symptoms or other incapacitating or embarrassing symptoms (e.g., fear of falling in the elderly; fear of incontinence).
C. The agoraphobic situations almost always provoke fear or anxiety.
D. The agoraphobic situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety.
E. The fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations and the sociocultural context.
F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 months or more.

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DSM V criteria for Social Anxiety

- fear or anxiety specific to social settings, in which a person feels noticed, observed, or scrutinized.
- individual will fear that they will display their anxiety and experience social rejection,
- social interaction will consistently provoke distress,
- social interactions are either avoided, or painfully and reluctantly endured,
- the fear and anxiety will be grossly disproportionate to the actual situation,
- the fear, anxiety or other distress around social situations will persist for six months or longer and
- cause personal distress and impairment of functioning in one or more domains, such as interpersonal or occupational functioning,
- the fear or anxiety not attributed to a medical disorder, substance use, or adverse medication effects or another mental disorder

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Specific Phobia DSM V

- **Unreasonable, excessive fear**: The person exhibits excessive or unreasonable, persistent, and intense fear triggered by a specific object/situation
- **Immediate anxiety response**: The fear reaction must be out of proportion to the actual danger and appears almost instantaneously when presented with the object/situation
- **Avoidance or extreme distress**: The individual goes out of their way to avoid the object or situation or endures it with extreme distress
- **Life-limiting**: The phobia significantly impacts the individual's school, work, or personal life.
- **Six months duration**.
- **Not caused by another disorder;** rule out agoraphobia, OCD, and separation anxiety disorder before diagnosing a specific phobia disorder.
- **Types:** Natural/environment type (thunder, water), Injury type (needles, dentist), Animal type (dogs, snake, insects), Situational (planes, closed places)

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DSM V Post -Traumatic Stress Disorder (PTSD)

Exposure to a traumatic event (either experiencing or witnessing event)

- **Intrusive Memories (1 or more)**

Recurrent distressing memories of event, flashbacks, nightmares, emotional distress in response to triggers

- **Avoidance (1 or more)**

Avoid thinking or talking about the traumatic event: Avoids places, activities or people that are reminders of traumatic event

- **Negative Changes in Feelings/Mood (2 or more)**

Negative thoughts about yourself/other people/the world, hopelessness, memory difficulty, difficulty maintaining close relationships, detached from family/friends, lack of interest, difficulty experiencing + emotions, emotional numbness

- **Changes in Arousal/Reactivity (2 or more)**

Startled/easily frightened, always being on guard for danger, self-destructive behavior, trouble sleeping/concentrating, irritability/anger outburst or aggressive behavior, guilt/sham

Symptoms must be present for 1 month or longer, cause much distress and/or interfere significantly with areas life; not due to a medical condition/ substance use

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DSM V

Obsessive Compulsive Disorder

A. Presence of obsessions, compulsions, or both:

Obsessions
1. Intrusive/unwanted recurrent/ persistent thoughts, urges, or impulses causing marked anxiety or distress.

2. Attempts to ignore/ suppress unwanted thoughts, urges, or images, or to neutralize them with some other thought or action (compulsion)

Compulsions
1. Repetitive behaviors (e.g., hand washing, ordering, checking)/mental acts (e.g., praying, counting, repeating words silently), in response to an obsession/rigidly applied

2.The behaviors/mental acts are aimed at preventing/reducing anxiety or distress

B. The obsessions/ compulsions are time-consuming (e.g., take more than 1 hour per day) and cause significant distress/ impairment in social, occupational, or other important areas of functioning.

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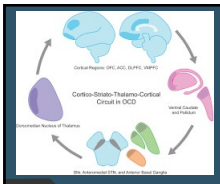

Etiology/Neurobiology of Anxiety (Stahl, S. 2013)

-Anxiety and fear symptoms (e.g., panic, phobias) are regulated by an amygdala-centered circuit

- Worry (anxious misery, apprehension, expectations, obsessions) is regulated by the cortico-striato-thalamo-cortical (CSTC) loop

Neurotransmitters dysfunction involved in anxiety disorders: Serotonin (5HT), GABA (under activate), glutamate, corticotropin-releasing factor (CRF), and norepinephrine (NE)

Hippocampus-memory plays a role in determining behavior in response to anxiety AE: avoidance; hypothalamus mediates stressful occurrences

Fear Network: Limbic System involved in anxiety disorders specifically amygdala (hyperactive), increased activity in the anterior Insula, and altered activity in the anterior cingulate cortex (ACC)

FMRI Neuroimaging studies show greater activation of amygdala in subjects with anxiety disorders compared to controls

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FDA Medications Approved for Anxiety Disorders

1) FDA Approved for Generalized Anxiety Disorder (1st line SSRIs)

SSRI: Paroxetine (Paxil) and Escitalopram (Lexapro)

SNRI: Duloxetine (Cymbalta) and Venlafaxine (Effexor)

Benzodiazepines: Alprazolam (Xanax) not recommended

- **2) FDA Approved for Panic Disorder (1st line SSRIs)**
- **SSRI:** Fluoxetine (Prozac), Paroxetine (Paxil), Sertraline (Zoloft)
- **SNRI:** Venlafaxine (Effexor)
- **Benzodiazepines:** Alprazolam (Xanax-IR), Clonazepam (Klonopin), no recommended

- **3) FDA Approved for Social Anxiety Disorder**
- **SSRI:** Sertraline (Zoloft), paroxetine (Paxil) , and fluvoxamine (Luvox)
- **SNRI:** Venlafaxine (Effexor)

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FDA-Approved Medications for Non-specific Anxiety

- **5HT partial agonist:** buspirone (Buspar)
- **Antihistamine:** hydroxyzine (Vistaril)
- **Benzodiazepines**-alprazolam (Xanax), lorazepam(Ativan),diazepam (Valium), chlordiazepoxide (Librium)

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Used off Label for Anxiety

SSRI/SRM: Vortioxetine (Trintellix)

- **SSRI/partial 5Ht receptor antagonist:** Vilazodone (Viibryd)
- **SNRI:** Duloxetine (Cymbalta)
- **TCAs:** Amitriptyline (Elavil) , Desipramine (Norpramin) , Doxepin. Imipramine (Tofranil),Nortriptyline (Pamelor)
- **NaSSA:** Mirtazapine (Remeron)
- **Beta Blocker** -propranolol
- **GABAnergic**-Gabapentin
- **Antipsychotic:** Quetiapine(Seroquel)

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Medications for PTSD/OCD

- **1) FDA Approved Medications for PTSD**
- **SSRI:** Sertraline (Zoloft), Paroxetine (Paxil)
- **OFF-Label EBP**
- **SSRI:** Fluoxetine (Prozac) **SNRI:** Venlafaxine (Effexor)
- **Anti-hypertensive:** Prazosin (Minipress) for nightmares/improve sleep

Avoid: Benzodiazepines/Stimulants (Risk of SUD, worsen symptoms)

- **2) FDA Approved Medications for OCD**
- **SSRI:** Fluoxetine (Prozac), Fluvoxamine (Luvox), Paroxetine (Paxil), Sertraline (Zoloft)
- **TCA:** Clomipramine (Anafranil)
- **Off Label EBP**
- **SSRI:** Citalopram (Celexa), Escitalopram (Lexapro),
- **SPARI**: Vilazodone (Viibryd)

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Anxiety Treatments

- **Cognitive Behavioral Therapy (CBT):** Teaches skills to interrupt and change automatic thoughts/behaviors; teaches specific CBT skills and concepts; identifies/helps change distorted thinking patterns, emotional responses, and behaviors
- -**Exposure Therapy:** Helps confront feared stimuli (safe environment) external (feared objects, activities, situations)/internal (feared thoughts, physical sensations).
- - **Eye Movement Desensitization and Reprocessing (EMDR)** Therapy **(PTSD)-Patients recall distressing experiences while simultaneously performing bilateral stimulation, side-to-side eye movement or tapping either side of the body.**

-**Psychoeducation**

- -**Mindfulness**
- -**Yoga**
- -**Diaphragmatic Breathing/ Progressive Relaxation Techniques**
- -**Acupuncture**

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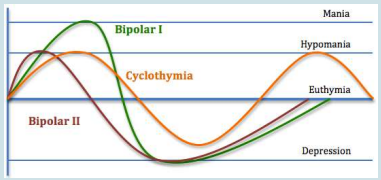
Mood Disorder Spectrum

- Major Depression Disorder
- Bipolar 1
- Bipolar 2
- Cyclothymia



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Major Depressive Disorder

According to National Institute of Mental Health 2020
- ~ 21 million adults in the United States had at least one major depressive episode; 8.4 % of US adults
- MDD is higher among women (10.5 %) compared to men (6.2 %)

~4.1 million adolescents aged 12 to 17 in the United States had at least one major depressive episode; 17.0% of the U.S. population aged 12 to 17 (NIMH 2020)

According to CDC 2018
- Depression is the leading cause of disability in the US among persons ages 15-44

Depression was indicated on 10.6 % of physician office visits medical records (CDC 2018)

Depression was indicated on 11.2 % of emergency room medical records (CDC 2018)

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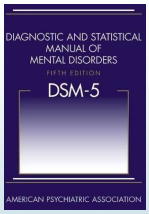
- **Major Depressive Disorder**
- DSM-5
- **5 or more symptoms**, present during the same 2-week period, most of the day, nearly everyday
- One must be either **depressed mood** or **decrease interest/apathy**
- **Plus**
  - **Sleep disturbances (insomnia/hypersomnia)**
  - **Loss of energy/fatigue**
  - **Decrease concentration**
  - **Weight gain/loss, appetite changes**
  - **Feelings of guilt/worthlessness**
  - **Psychomotor agitation/retardation**
  - **Thoughts of death/suicide**



- **REMEMBER**
- SIGECAPS
- Sleep, interests, guilt, energy, concentration, appetite, psychomotor, suicide

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Subtypes MDD/Bipolar

Subtype	MDD	Bipolar Disorder	Criteria
Seasonal Pattern	✓ yes	✓ yes	Episodes regularly at same time of year
Rapid Cycling	No	✓ yes	4 episodes within past year
Mood congruent psychotic features	✓ yes	✓ yes	Delusion/hallucinations consistent with mood (guilt/death)
Mood incongruent psychotic features	✓ yes	✓ yes	Delusion/hallucinations inconsistent with mood episode
Mixed feature	✓ yes	✓ yes	3 manic symptoms during depressed episode; 3 depressive symptoms during man manic episode
Catatonia	✓ yes	✓ yes	Physical immobility
Melancholic features	✓ yes	✓ yes (depressive episode)	Lack of pleasure in any activity and 3 + quality of mood/worsening mood in AM, loss of appetite/wt loss, guilt, early AM, Wakening, psychomotor retardation/agitation, guilt
Atypical Feature	✓ yes	✓ yes	Unusual symptoms
Peripartum onset	✓ yes	✓ yes	Onset during pregnancy or 4 weeks post partum
With anxious distress	✓ yes	✓ yes	At least 2 symptoms of anxiety
Suicide risk Severity	✓ yes	✓ yes	Suicide ideation, plan or other risk factors present

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Degrees of Depression

Severity/course specifiers

- ✓ **Mild**
- ✓ **Moderate**
- ✓ **Severe , with or without psychosis**
- ✓ **Partial remission**
- ✓ **Full remission**
- ✓ **Unspecified**

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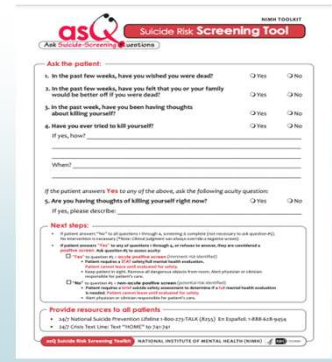

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Monoamine Hypothesis of Depression

Classic Monoamine Hypothesis

Depression occurs when normal amounts of monoamine transmitters (**serotonin 5HT, norepinephrine, NE dopamine DA)** become reduced, disrupted or dysfunctional.

The Monoamine Receptor Hypothesis

The monoamine receptor hypothesis takes the classic monoamine hypothesis and postulates decreased activity of monoamine neurotransmitters causes upregulation of postsynaptic monoamine neurotransmitter receptors, leading to depression.

Stahl, Stephen M.. Stahl's Essential Psychopharmacology . Cambridge University Press. Kindle Edition (2013)

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Other Neurotransmitters in Depression

- Glutamate Hypothesis
  - NMDA is one of the receptors for glutamate, the major excitatory amino acid in the brain
  - NMDA receptor antagonist has antidepressant action
- **GABA**
  - GABA levels (CSF) decreased in 40 % of depressed patients
  - Neuroimaging studies- decreased GABA receptors in Pre -Frontal Cortex
  - Dopaminergic neurons mediate via GABA receptors
  - (Stahl 2013)

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Neuro-Endocrine Factors (Stahl 2013)

Hypothalmic-pituitary-adrenal (HPA) Axis

- High levels of serum, CSF, and urine cortisol have been found in depressed patients
- Overactive HPA axis leads to cognitive dysfunction and low mood
- HPA axis abnormalities involved in chronic stress
- Increased # of neurons in the hypothalamus; theorized to increase activity in response to chronic stress, causing a disruption in the negative feedback system
- Excessive cortisol release may lead to hippocampal/amygdala atrophy
- HPA dysregulation leads to neurotropic dysregulation; leading to functional brain abnormalities, damage to synapse/neurons causing structural brain abnormalities > cognitive decline

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MDD

- Untreated depressive episodes are self-limiting (lasting 6-12 months)
- MDD cyclic; episodes more frequently as disorder progresses (risk of another MDD episode ~ 60 % after the first episode) (NAMI , 2018)
- Early treatment is of the essence to prevent severity
- ~ 15 % of persons with MDD commit suicide (NAMI, 2018)
- ~ 65-70 % of persons with MDD respond to antidepressants; increased outcomes with adjunct psychotherapy (NAMI, 2018)

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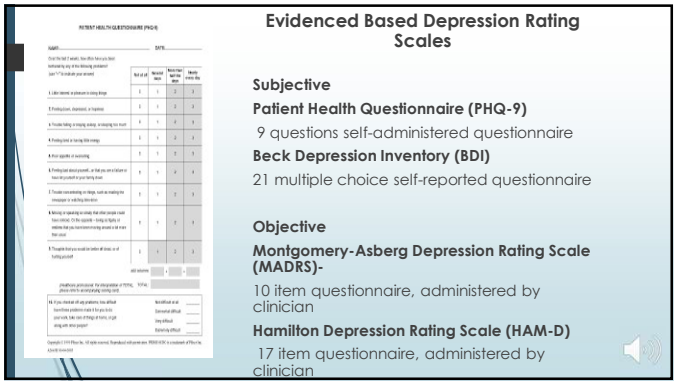

Evidenced Based Depression Rating Scales

Subjective

Patient Health Questionnaire (PHQ-9)

9 questions self-administered questionnaire

Beck Depression Inventory (BDI)

21 multiple choice self-reported questionnaire

Objective

Montgomery-Asberg Depression Rating Scale (MADRS)-

10 item questionnaire, administered by clinician

Hamilton Depression Rating Scale (HAM-D)

17 item questionnaire, administered by clinician

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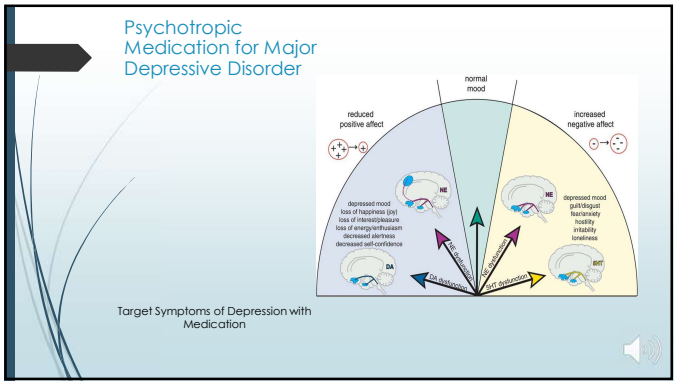

Psychotropic Medication for Major Depressive Disorder

Target Symptoms of Depression with Medication

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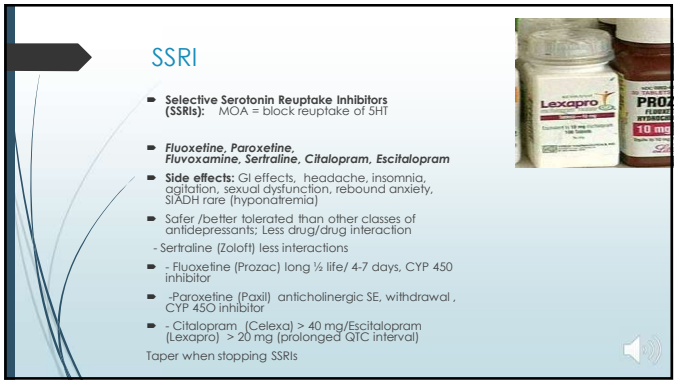

SSRI

- **Selective Serotonin Reuptake Inhibitors (SSRIs):** MOA = block reuptake of 5HT
- ***Fluoxetine, Paroxetine, Fluvoxamine, Sertraline, Citalopram, Escitalopram***
- **Side effects:** GI effects, headache, insomnia, agitation, sexual dysfunction, rebound anxiety, SIADH rare (hyponatremia)
- Safer /better tolerated than other classes of antidepressants; Less drug/drug interaction
  - Sertraline (Zoloft) less interactions
- - Fluoxetine (Prozac) long ½ life/ 4-7 days, CYP 450 inhibitor
- -Paroxetine (Paxil) anticholinergic SE, withdrawal , CYP 450 inhibitor
- - Citalopram (Celexa) > 40 mg/Escitalopram (Lexapro) > 20 mg (prolonged QTC interval)

Taper when stopping SSRIs

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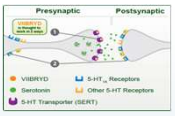
SPARIs



- **Serotonin partial agonist/reuptake inhibitors (SPARIs)**
  Vilazodone (Viibryd) ,Vortioxetine, (Trintellix)
- SE: GI disturbances, headaches, dizziness, fatigue, insomnia, bruising/ bleeding, sexual dysfunction, SIADH, hyponatremia
- (lower risk of weight gain and sexual side effects than the SSRI or SNRI)
- Medication expensive
- Patients with diagnosed or undiagnosed bipolar or psychotic disorders may be more vulnerable to CNS-activating actions of serotonergic antidepressants

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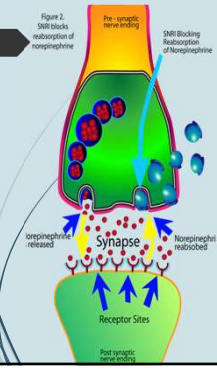
SNRI



SNRI- Serotonin and Norepinephrine Reuptake Inhibitors

- MOA- Serotonin–norepinephrine reuptake inhibitors (SNRIs): block reuptake of 5HT and NE
- Venlafaxine (Effexor); Duloxetine (Cymbalta) , Desvenlafaxine (Pristiq), Levomilnacipran (Fetzima)
- SE: Nausea, insomnia, dry mouth, headache,, nervousness, sedation, diarrhea, decreased appetited, increased blood pressure (dose dependent) sexual dysfunction, weight gain, SIADH, hyponatremia (rare), bleeding risk with NSAIDS
- ✓ Discontinuation syndrome (dizziness, nausea, vomiting, flulike symptoms, anxiety, irritability) Do not stop abruptly
- ✓ Taper when stopping SNRIs to avoid withdrawal symptoms
- ✓ B/P should be controlled in patients with hypertension
- ✓ Duloxetine FDA approved for neuropathy, chronic m/s pain, fibromyalgia
- ✓ Do not use with uncontrolled angle closure glaucoma
- ✓ Caution in history of seizures, heart disease, bipolar disorder

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Atypical Antidepressants

- Norepinephrine Dopamine Reuptake Inhibitor (NDRI)
- MOA: dual inhibition of norepinephrine and dopamine reuptake

- **Bupropion (Wellbutrin)**
- SE: dry mouth, constipation, nausea, weight loss, anorexia, insomnia, dizziness, headache agitation, anxiety, tremor, diaphoresis, hypertension (most SE are immediate, often go away with time)
- ✓ Bupropion is activating; does not have side effects of sexual dysfunction, weight gain (weight neutral) , or sedation
- ✓ **Lowers seizure threshold:** Higher incidence for immediate-release than for sustained-release; increased risk with doses above recommendations. **Do not use** with any other form of bupropion, history of seizures, eating disorders, discontinuing from ETOH/sedative/anticonvulsive medication, head injury, or nervous system tumor or other medications with increased seizure risk (lithium, TCAs, some antipsychotics, phenothiazines)
- ✓ Bupropion SR FDA approved for nicotine addiction
- ✓ Can be added to SSRIs to treat partial responders
- ✓ Used as augmenting agent to mood stabilizers/atypical antipsychotics for bipolar depression
- ✓ Stopping medication: tapering is suggested to avoid withdrawal (not well documented)

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Atypical Antidepressant

- Noradrenergic and specific serotonergic antidepressant (NaSSA)
- MOA: serotonin, NE, receptor antagonist; alpha 2 antagonist (noradrenaline and specific serotonergic agent dual serotonin/NE agent (boost 5HT/NE neurotransmitters, blocks alpha 2 adrenergic receptor/increasing NE neurotransmission/increasing 5HT neurotransmission, blocks H1 histamine receptors
- **Mirtazapine (Remeron)**
- SE: dry mouth, constipation, ***increased appetite, weight gain***, sedation, dizziness, abnormal dreams, confusion, change in urinary function, hypotension, flu-like symptoms (low WBC/granulocyte count)
- ✓ SE dose dependent; sedation at lower dose/activation at higher dose
- ✓ Use in caution in history of seizures (rare incident), may induce mania (rare), liver/renal/cardiac impairment
- ✓ Monitor BMI, weight gain; if 5 % or more weight gain evaluate for metabolic syndrome/ consider switching to another antidepressant

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Atypical Antidepressants

- SARI Serotonin 2 antagonist/reuptake inhibitor (antidepressant/hypnotic)
- Off label: primary/secondary insomnia (improve insomnia in other psychiatric conditions) and anxiety
- MOA: Blocks 5HT 2A receptors (strong) ; blocks 5HT reuptake pump
- **Trazodone (Desyrel/Oleptro)**
- SE: N/V, edema, blurred vision, constipation, dry mouth, dizziness, sedation, fatigue, headache, incoordination, tremor, hypotension, syncope, rare rash, SB (long term), priapism (rare), seizures(rare), induction of mania (rare)
- ✓ Taper recommended when stopping medication
- ✓ Trazodone may increase digoxin/phenytoin concentrations
- ✓ Additive effects with trazodone/other CNS depressants
- ✓ Caution with history of seizures

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Tricyclic Antidepressants TCAs

- TCAs MOA: blocks reuptake of norepinephrine/inhibits serotonin reuptake pump; antagonists at 5HT2A/5HT2c receptors; antagonist at H1-histaminic, a1-adrenergic and muscarinic cholinergic receptors; blocks voltage-sensitive sodium channels (overdoses coma seizures, arrhythmia, death)
- **SE:** blurred vision, constipation, urinary retention, increased appetite, dry mouth, nausea, diarrhea, weight gain, fatigue, weakness, dizziness, sedation, headache, anxiety/nervousness, restlessness, sexual dysfunction, diaphoresis, rash, itching
- Paralytic ileus, hyperthermia (TCAs +anticholinergic medications), lowers seizure threshold (rare seizures, orthostatic hypotension, ***sudden death, arrhythmias, tachycardia, QTC prolongatio***n, hepatic failure, extrapyramidal symptoms (EPS), increase intraocular pressure, induction of mania (rare)

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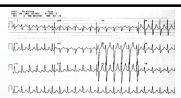
TCAs



- Baseline EKG for patients over 50 years old, family history of QTc prolongation
- Assess prior to start of TCA for overweight/obesity, diabetes, dyslipidemia (treat)
- Monitor weight/BMI during treatment; if > 5% of initial weight, evaluate for diabetes/dyslipidemia/or consider switching to another medication
- Electrolyte disturbances (diuretics) Base line K, Mg and periodic checks
- Do not use if patient recovering from MI, with other agents that prolong QTc, history of QTc prolongation, cardiac arrhythmia, recent MI, or uncompensated heart failure
- Amitriptyline (Elavil), Amoxapine., Desipramine (Norpramin)Doxepin, Imipramine (Tofranil), Nortriptyline (Pamelor) Protriptyline, Trimipramine

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MAOI

MOA: Irreversibly blocks monoamine oxidase (MAO) from breaking down norepinephrine, serotonin, boosting noradrenergic, serotonergic, and dopaminergic neurotransmission (chemically related amphetamine, may have some stimulant-like action).

SE: agitation, anxiety, **insomnia,** weakness, sedation, dizziness, constipation, dizziness, dry mouth, nausea, diarrhea, weight gain, **sexual dysfunction**, **orthostatic hypotension (dose dependent)**

Hypertensive Crisis (especially when used with tyramine-containing foods/prohibited drugs, induction of mania, seizures, hepatotoxicity

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MAOIs
socarboxazid (Marplan)

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

- Overdose: dizziness, sedation, ataxia, headache, insomnia, restlessness, cardiovascular effects, confusion, respiratory depression or coma
- ***CAN CAUSE FATAL SEROTONIN SYNDROME*** DO NOT USE WITH OTHER SEROTONERGIC ANTIDEPRESSANTS; NEED 2 WEEK WASHOUT PRIOR TO STARTING ANOTHER MEDICATION
- Hypertensive Crisis with headache, intracranial bleeding, and death may result if combined with sympathomimetic drugs (amphetamines, cocaine, dopamine, epinephrine, methyldopa, levodopa
- Do not combine with another MAOI, ETOH, or guanethidine
- Require low tyramine diet (dried, aged, smoked stored meats/poultry/fish, aged cheese, tap beer, wine, soy products/tofu
- Possible interactions with OTC cough/cold medications, antihypertensives

Do not use : with diuretic, dextromethorphan, cardiovascular/cerebrovascular disease, severe/frequent headaches, elective surgery with anesthesia, history of liver disease/abnormal liver function test, non-adherent with low tyramine diet, allergy to tranylcypromine

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Augmentation Medications

2nd generation antipsychotics FDA approved for augmentation

- Aripiprazole (Abilify)- energy/motivation
- Quetiapine (Seroquel) extended release (sleep)
- Brexpiprazole (Rexulti)

- **OFF label but supported by literature:**
  - Lithium
  - Buspirone
  - Psychostimulants (amphetamines and derivatives)
  - Thyroid supplementation

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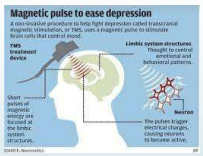
Transcranial Magnetic Stimulation (TMS)

- *** 30 % of people diagnosed with depression have no response to antidepressant treatment (TRD)**
- ***Approximately 20 % stop taking antidepressants because of side effects**



- TMS
- TMS is a FDA-Cleared Device used for MDD, severe, without psychosis who have failed to achieve sufficient improvement from a single antidepressant trial in current episode (second line)
- TMS is FDA-Cleared for Obsessive Compulsive Disorder (OCD), migraine headaches, and smoking cessation.

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TMS Neuromodulation

-Stimulates circuits; induces neuroplasticity

-Works by using MRI-strength magnetic field pulses; delivers magnetic pulses the cortex via a stimulating coil, applied directly the head

-Stimulator-generating brief pulses of strong electrical currents through a stimulator coil

-Magnetic field generated at the coil passes through scalp/skull inducing electrical current in underlying tissue which depolarizes neurons

-Activates nerve cells in the brain, causing them to normalize neurotransmitter function

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TMS

- ✓ Does not circulate in the blood throughout the body, does not involve surgery/anesthesia
- ✓ No known adverse effects on cognition/memory
- ✓ No systemic side effects such as weight gain, sexual dysfunction, nausea, dry mouth, and sedation
- ✓ TMS therapy is a safe procedure that allows patients to do their usual activities after each treatment, like work or driving without interruption
- ✓ Course of treatment typically consists of 5 treatments per week over a 6-9 week period, for an average of 36 total treatments
- ✓ Each treatment lasts approximately 40 minutes

Transcranial Magnetic Stimulation (TMS) Therapy involves the use of MRI-strength magnetic fields to stimulate nerve cells in the brain. First used in 1985. TMS has been utilized by researchers around the world to help understand the function of parts of the brain

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TMS

- Absolute contraindication: movable implanted ferromagnetic metal implants (aneurysm clips/coils, stents, cochlear implants, bullet fragments) less than 30 cm from coil
- Risk for Seizures: History of seizure disorder or 1st degree relative with seizure disorder, medications/substance use/caffeine (lowering the seizure threshold)
- Most insurance policies covers TMS; 2-4 antidepressants with 2 adjunct medications and psychotherapy (CBT) or patient is candidate for ECT and TMS is a less invasive treatment option for patient
- Sustained response rate 50 % after 1 year of treatment
- ~ 60 % response rate; 40 % remission rate (after 12 months)

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Electroconvulsive Therapy (ECT)

- Induce a generalized seizures via electrical current to the brain
- Stimulus is applied through electrodes placed unilateral/bilaterally to frontotemporal area
- Patient under general anesthesia (methohexital/succinylcholine)
- Duration of motor seizure should be > 20 seconds; EEG last ~ 40 sec
- Treatment 3 times weekly (M-W-F): Total 12 treatments
- MDD, severe with/without psychosis, catatonia, TRD, suicidality, acute mania, acute schizophrenia
- Lifesaving treatment for many (catatonia)
- Maintenance ECT recommended; ~ 52 % of persons relapse within 6 months
- MOA: unknown; epileptic patients postictal mood improves
- SE: memory loss (transient) /confusion, muscle pain, headaches
- Efficacy rate ~ 90 % for severe depression (Petrides G, et al.)

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Esketamine/Spravato

- FDA approved March 2019
- Esketamine is S form of Ketamine MOA: NMDA antagonist facilitates glutamate release; growth of new synapses
- **Treatment resistant depression (TRD) and MDD with acute suicidal ideation or behavior (MDSI)**
- **Nasal spray taken with an oral antidepressant; rapid efficacy**
- Weeks 1 to 4: Administer twice per week; Weeks 5 to 8: Administer once weekly (individualized to lowest dose to maintain remission/response)
- Administered by certified physician office; patient monitor 2 hours after administration
- 69% response rate and a 52% remission rate verses placebo; 52% and 31% response and remission rates (Daly, 2019)
- Esketamine/antidepressant decreased the risk of relapse by 51% among patients who achieved remission; 70% among those who achieved response compared with antidepressant and placebo treatment (Daly, 2019)

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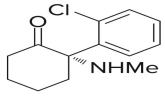
Esketamine

- **SE:** dissociation, hallucinations (within first 40 minutes of treatment) dizziness, nausea, sedation, vertigo, numbness, anxiety, metallic taste in the mouth, headache, lethargy, increased blood pressure, vomiting and urinary tract symptom
- **Black Box Warning: Risk for sedation and dissociation after administration**. ***Potential for abuse and misuse***

Contraindications: Aneurysmal vascular disease, A/V malformation intracerebral hemorrhage

Figure 1 Chemical Structure of Esketamine



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Other therapies for MDD

- **Psychotherapy:** cognitive behavioral therapy or interpersonal therapy
- **Exercise :** helpful for mild/moderate depression.
- **Light therapy:** using a light box; exposes light to regulate melatonin
- **Alternative approaches** : acupuncture, mindfulness/meditation, and nutrition as part of the treatment plan

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Mental Status Exam

- Appearance: well-groomed or unkempt, dressed appropriately
- Speech: normal (regulate, rate, rhythm) or pressured, loud or monotoned
- Behavior: calm, cooperative or guarded, tearful
- Mood: subjective= irritable, elevated, anxious, depressed
- Affect: objective= broad, full, blunted, expansive, restricted
- Thought Process: logical, linear, goal-directed, circumstantial, tangential, circumstantial, flight of ideas, loose associations, thought blocking
- Thought Content: suicidal/homicidal ideation/plan/intent, delusions, ideas of reference, paranoia, obsessions, hallucinations
- Cognition: Alert/oriented times 4
- Attention/Concentration: Serial 7s
- Abstract thinking: apple and orange
- Memory: recall of 3 objects after 5 minutes; Fund of Knowledge: Current events
- Insight: Awareness of illness/need for treatment
- Judgment: show good judgment (what they would do if smelled smoke in a crowd)

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