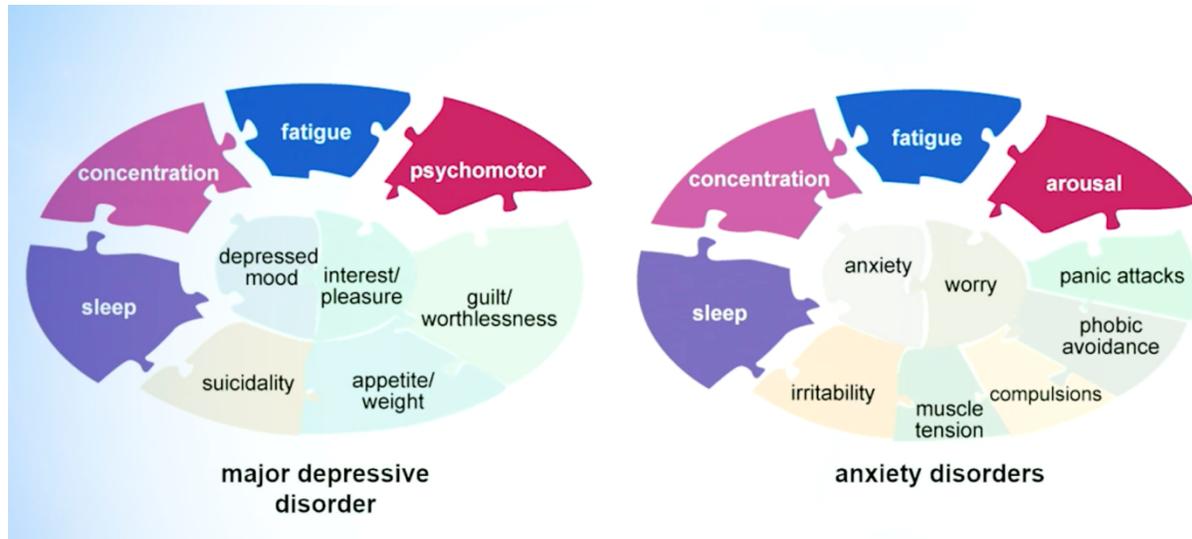


Anxiety, Trauma, and Treatment

Overlap of major depressive disorder and anxiety disorder



- Depression with Anxiety can make it more difficult to treat

Generalized Anxiety Disorder

- At core: generalized anxiety, fear and generalized worry
- Concentration
- Fatigue
- Arousal
- Sleep
- Irritability
- Muscle tension

Panic disorder

- At core: anticipatory anxiety/fear and worry about panic attacks
- Unexpected panic attacks
- Phobic avoidance / behavior change

Social anxiety disorder

- At core: social performance/anxiety/fear, and worry about exposure
- expected panic attacks
- Phobic avoidance / behavior change
- First line of treatment is alpha-2-delta ligand

PTSD

- At core: anxiety/re-experiencing and worry
- Avoidance
- Arousal
- Sleep problems
- Many co-morbid conditions

Anxiety

- Fear
 - Panic
 - Phobia
 - Amygdala centered circuit
 - The amygdala is the place where suicidality and worthlessness
- worry
 - anxious misery
 - apprehensive expectations
 - obsessions
 - cortico-striato-thalamo-cortical circuit

Fear responses

- flight, fight, or freeze

endocrine and hypothalamus

- increase cortisol
- increase coronary artery disease
- increase stroke
- increase diabetes

Breathing

- parabrachial nucleus
 - The parabrachial nucleus (PBN) regulates changes in respiration, which can occur during fear response. This regulation is activated by the amygdala. Excessive activation of the PBN can lead to an increased rate of respiration and symptoms such as shortness of breath or a sense of being smothered.
- increase respiratory rate
- increase shortness of breath
- increased asthma

Autonomic output

- cardiovascular
- increased atherosclerosis
- increase cardiac ischemia
- increase blood pressure
- decreased heart rate variability
- increase MI
- sudden death

The Hippocampus:

- activates fear from memory

We want to modify the amygdala centered circuit:

- 5HT, GABA, glutamate, CRF/HPA, NE, and voltage gated channels

We want to modify the cortico-striato-thalamo-cortical circuit “worry loop”:

- 5HT, GABA, DA, NE, and voltage gated channels

Three main Classes of Drugs for Anxiety

- Benzodiazepines
 - Blocks the amygdala reduce fear
 - Can lead to dependence
 - Increases GABA via positive allosteric modulation
 - GABA interneuron in the cortex add a benzo reduces worry
- Alpha-2-Delta Ligands
 - *Gabapentin*
 - *Pregabalin*
 - They work at zones of the brain that the amygdala activates reduce fear and worry
 - There is another channel that is voltage dependent it is a voltage sensitive N or P/Q Calcium channel. Has glutamate inside, get thrown out and calcium will go into the cell. There is a Alpha-2-Delta Ligand which will stick to these channels and causes the calcium channel to shut so no more glutamate release.
 - Helps with epilepsy, pain and anxiety (glutamate in the wrong part of the brain do this)
 - Suicide warning, slight dependence, weight gain, and sedation
 - Off-label in the US
- Serotonergic Agents (reuptake inhibitors and 5HT1A agonists and Partial agonists)
 - Causes the raphe neuron to desensitize the amygdala to reduce fear
 - The raphe innervate the parts of the brain that causes worry and desensitizes them

Two types of GABA mediated Inhibition

- GABA is in the GABA neuron, glial cell is making a neuroactive steroid. In post synapse there are GABA receptors. Two types:
 - GABA a (a1-a3) have a phasic inhibition
 - Benzodiazepines can modify, benzo binding site
 - Neuroactive steroid can modify
 - GABA a (a4-6) tonic setting the tone, tonic inhibition.
 - Neuroactive steroid can modify helps GABA

Fear and Autonomic Hyperarousal

- Fear, panic, sweating, tachycardia, hyperarousal, and nightmares
- Norepinephrine is the neurotransmitter to focus on
- Use Alpha 1 Antagonists or NET inhibitor
 - Desensitizes the receptors

Fear Conditioning vs. Fear Extinction

- Fear extinction is when you forget your fear, can be difficult
- Amygdala has input from VMPFC, hippocampus, sensory cortex, and thalamus
- Traumatic event will make the amygdala neurons who are sensitive
- Fear extinction will create a fear inhibition this can happen through therapy or exposure.

- Drugs used to induce a mental state with psychotherapy to mess up the memory and remodel it. MDMA (ecstasy)

Beta Blocker and Opiates Prevent Fear Conditioning and Reconsolidation of fear

- If you get prescribed early enough.

Medication Treatments for Anxiety/Stress Disorder Subtypes				
	GAD	Panic disorder	Social anxiety disorder	PTSD*
Benzodiazepine	X	X		
Alpha-2-delta ligand	X	X	X	
SSRI/SNRI	X	X	X	X
5HT1A partial agonist	X			
Other	Mirtazapine Trazodone TCAs Hydroxyzine	Mirtazapine Trazodone MAOIs	Beta blockers	Alpha 1 antagonists In testing: MDMA and brexpiprazole

*Pharmacological treatments are not as effective for PTSD as they are for anxiety disorder subtypes

NRI's norepinephrine reuptake inhibitors also called norepinephrine transport inhibitors (Stahl, 2020). The administration of a norepinephrine transporter (NET) inhibitor can block noradrenergic hyperactivity, which can have the downstream effect of downregulating β 1-adrenergic receptors, this leads to the alleviation of anxiety and stress-related symptoms.