These Unnerving times....

Management of Anxiety Disorders in our increasingly anxious world

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Objectives

- Review epidemiology of anxiety disorders and barriers to care
- Review medications used to treat anxiety related disorders
- Discuss non-pharmacological treatment options
- Present diagnostic criteria for the primary anxiety disorders that affect the adult population [reference slides]
Anxiety

- A state of hypervigilence, resulting in autonomic hyperactivity, motor tension.

- Emotions:
  - originate in the limbic system (amygdala)
  - Influenced by the Prefrontal Cortex

The Limbic System

5HT – NE – GABA
The Anxiety Disorders

- Generalized Anxiety Disorder
- Social Anxiety Disorder
- Panic Disorder
- Specific Phobia
Epidemiology of Anxiety Disorders

- Experienced by up to 1/3 of the US population
- A leading cause of disability worldwide
- Highly comorbid
  - 50% of chronic pain patients screen positive for at least one AD
  - 35% of cardiac patients meet criteria for one AD
  - A relationship between baseline anxiety and Type II diabetes has been established
- Associated with a poorer quality of life
AD Management Challenges: access to care

- Demand for psychiatric providers: HIGH
- More severe mental disorders often prioritized
- Majority of depression/anxiety patients are treated in primary care
- Emergency Department use – on the rise
AD Management Challenges: clinician shortages

- 77% of US counties report a “severe deficiency of psychiatrists”
- 59% of the 30,451 currently practicing psychiatrists are over age 55
- Oregon: 9.8 psychiatrists per 100,000 people
- About 50% of Oregon’s mental health need is currently being met
Anxiety Management Challenges: continued

- Collaborative care barriers
- A difficult condition to treat:
  - Often chronic
  - Regarding medication:
    - Prefer “rescue only” therapy
    - Have a fear of all medications
    - Unrealistic expectations for medication
Anxiety appointments: a learning opportunity

- The clinician can learn about their patient
  - “How can I be helpful?”
  - “Are you interested in medication?”

- The patient can learn about anxiety:
  - Part of the human experience
  - Physiological response to danger/stress
Pharmaceutical Therapy Options

- Selective Serotonin Reuptake Inhibitors (SSRI)
- Serotonin-norepinephrine reuptake Inhibitors (SNRI)
- Serotonin multimodal/SPARI
- Tricyclic Antidepressants (TCA)
- Tetracyclic & unicyclic antidepressants
- Monoamine oxidase inhibitors (MAOIs)
- 5-HT$_{2A}$ antagonists
- Anxiolytics
The monoamine hypothesis of depression predicts that the underlying pathophysiologic basis of depression is a depletion in the levels of serotonin, norepinephrine, and/or dopamine in the central nervous system.

This hypothesized pathophysiology appears to be supported by the mechanism of action of antidepressants: agents that elevate the levels of these neurotransmitters in the brain have all been shown to be effective in the alleviation of depressive symptoms."

Anxiety Disorders: Medication Management

- Select agent with preferable side effect profile
- Start low
- Go slow
Selective Serotonin Reuptake Inhibitors (SSRIs)

- Inhibit the Serotonin Transporter (SERT)
  - Thought to limit reuptake of serotonin in presynaptic cells
  - Increase the concentration & activity of serotonin
- Side effects:
  - GI upset
  - headache
  - sleep disturbance (insomnia or hypersomnia
  - loss of libido/ED
  - Bone mineral changes in the elderly
Selective Serotonin Reuptake Inhibitors (SSRIs)

- **Fluoxetine** – oldest, longest half life, best for patients with compliance issues
- **Citalopram** – max dose 40mg due to QTc prolongation
- **Paroxetine** – short half life, weight gain, [Tamoxifen = ↑mortality]
- **Fluvoxamine** – sedation is common, caution with AAPs and Anticonvulsants
- **Sertraline** – best documented safety for cardiovascular patients, ↑GI side effects
- **Escitalopram** – least CYP450 activity = “plays well with others”
Selective Serotonin Reuptake Inhibitors (SSRIs)

Benefits of use:
- Safe to use
- Efficacy is validated in the medical literature
  - GAD
  - OCD
  - Panic Disorder
- Cost effective
- Broad spectrum of use

Drawbacks:
- Time to effect
- [side effects]

I'm sorry, I'm on Prozac. Was there something you wanted me to care about?
Serotonin-norepinephrine reuptake Inhibitors (SNRI)

- Bind both Serotonin (5HT) and Norepinephrine (NE) transporters
- Similar side effect profile to SSRI
  - + hypertension
- Similar NE/5HT effect to Tertiary Amine TCAs, but with better receptor affinity and fewer side effects
Serotonin-norepinephrine reuptake Inhibitors (SNRI)

1. Venlafaxine – short half life, weight gain
2. Duloxetine – effective with pain (arthritic), renal clearance
3. Desvenlafaxine – effective with pain (fibromyalgia), fatigue
Serotonin Multimodal & partial agonist reuptake inhibitor \((S-MM)\) \(\text{(SPARI)}\)

Relatively new anti-depressants

- **Vilazodone** (Viibryd) = SPARI & S-MM
  - \(5HT_{1A}\) activity = a unique mechanism of action
  - Possibly a faster therapeutic response time (1 week)
  - Not likely to cause weight gain or sexual dysfunction
  - Pancreatitis = risk

- **Vortioxetine** (Trintellix, formerly Brintellix) = S-MM
  - Effects five different 5HT receptors
  - Onset to effect 2-4 weeks
  - Also unlikely to cause weight gain, sexual dysfunction
Tricyclic Antidepressants

SNRI with less receptor selectivity: H1, Acetylcholine, alpha adrenoreceptor activity

- More anticholinergic side effects
- QTc Risk: Baseline EKG, avoid with cardiac arrhythmia
- LETHAL IN OVERDOSE
Tricyclic Antidepressants

**Secondary Amines** = NE receptor targets, side effects better tolerated

- a) Desipramine (highest cardiac risk)
- b) Nortriptyline

**Tertiary Amines** = 5HT and NE receptor targets

- a) Amitriptyline – post concussive syndrome headaches, chronic pain
- b) Imipramine
- c) Clomipramine – FDA approved for OCD
- d) Doxepin – strong antihistamine, can treat itching
Tetracyclic and Unicyclic Antidepressants

**Bupropion**
- Chemical structure similar to amphetamines
  - Side effects: weight loss, insomnia, anxiety
- FDA approved: MDD, Seasonal affective disorder, tobacco use disorder
- *No role in the treatment of anxiety disorders*
- Can treat sexual side effects of other anti-depressants
- Contraindications: seizure disorder, ETOH disorder, bulimia

**Mirtazapine**
- H1 receptor antagonism: weight gain, sedation
- Action on anxiety & insomnia is immediate
- No sexual side effects
Monoamine Oxidase Inhibitors

“MAOIs should be for the expert, especially if combining agents of potential risk (stimulants, trazodone, TCAs)” – Stahl’s Essential Pharmacology

- Irreversibly & non-selectively inhibit monoamine oxidase in the brain and gut
  - Prevent the breakdown of serotonin and
  - Serotonin syndrome = risk
- Tyramine dietary restrictions
- Used (not FDA approved) in panic and social anxiety disorders
- Selegiline – transdermal patch, receptor selectivity in the gut, triple action on serotonin, NE, and dopamine
- Phenelzine, Tranylcypromine, isocarboxazid
5-HT$_{2A}$ antagonists

- Popular until advent of SSRIs
- No tolerance, dependence
- Sedating – as a hypnotic indefinite use appears safe
  - **Trazodone**
    - primarily prescribed for **insomnia**
    - can boost effects of other antidepressants for anxiety/depression
    - sexual side effects unlikely
  - **Nefazodone** - black box warning = hepatoxicity
Anxiolytics:
H1 antagonists (antihistamines)

- Histamine blockade in the brain = sedation
- Effect is immediate (15 min, oral)
- Caution with long term use
  - relationship between anticholinergic activity and dementia risk
  - Hydroxyzine – also treats pruritus, contraindicated in early pregnancy
  - Diphenhydramine – can treat EPS, weight gain significant

Anxiolytics: Azapirones

Serotonin receptor partial agonist

- Often used as augmentation with SSRI, SNRI

1. Buspirone

- Shorter half life = BID or TID dosing
- No dependence / tolerance
- No sexual dysfunction issue
- Absorption is affected by food, consistency is important
- Side effects: dizziness, HA, nervousness
Anxiolytics: Benzodiazepines

- Sedative hypnotics
  - Potentiate GABA, primary inhibitory NT
  - Bind GABA$_A$ receptor
  - Inhibits neuron firing
  - CNS depression
    - Muscle relaxation
    - Sedation
    - Anxiolytic

My God, I hope it's an Ativan.
Anxiolytics: Benzodiazepines

- Advent Cerca 1960
- 1970 – the most common Rx prescribed in the world
- 1975 FDA restricted drug list
- 1999-2014 use spiked
- 2019: 15% of US population takes a BZD in any given year
- **Strong evidence** against long term use (over 2-4 weeks)
Anxiolytics: Benzodiazepines

- Clinical indication for:
  - Generalized Anxiety Disorder
  - Panic Disorder
  - Social Anxiety Disorder

- Anxiety with a predictable stimuli: air travel, MRI imaging, dental work

- No evidence to support:
  - Common practice: starting SSRI/SNRI + short BZD Rx
  - Long term use (over 4 weeks)
  - Long term = increased risk of dementia
Anxiolytics: Benzodiazepines

- Consider the idea of “rescue”

- Contraindications:
  - SUD
  - Suicidal Ideations
  - Neurocognitive disorders, TBI
  - Depression
  - Bipolar Disorder
  - Psychosis

Most of my anxiety comes from my fear of running out of Xanax.
Anxiolytics: Benzodiazepines

Drug accumulation

Withdrawal consideration

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Table 2: Clinical profile of benzodiazepines

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High potency benzodiazepines</strong></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>12-15</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>10-20</td>
</tr>
<tr>
<td>Triazolam</td>
<td>2-4</td>
</tr>
<tr>
<td>Etizolam (benzodiazepine analog)</td>
<td>2-4</td>
</tr>
<tr>
<td><strong>Low potency benzodiazepines</strong></td>
<td></td>
</tr>
<tr>
<td>Oxazepam</td>
<td>5-10</td>
</tr>
<tr>
<td>Temazepam</td>
<td>5-10</td>
</tr>
<tr>
<td><strong>Long half-life benzodiazepines</strong></td>
<td></td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>10-30</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>18-57</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>50-180</td>
</tr>
<tr>
<td>Diazepam</td>
<td>20-70</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 5: Withdrawal symptoms on benzodiazepine discontinuation

<table>
<thead>
<tr>
<th>System involved</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute withdrawal symptoms</td>
<td>Impaired concentration, Motor restlessness, tremor, muscle tension, sudden and abrupt twitching of muscles, inability to maintain gait</td>
</tr>
<tr>
<td>Cognitive</td>
<td>Increased heart rate, elevated blood pressure, increased sweating</td>
</tr>
<tr>
<td>Motor</td>
<td>Anxiety, apprehension, dysphoria, pessimism, altered sleep-wake cycle</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Generalized tonic-clonic seizures, hyperpyrexia, psychosis</td>
</tr>
<tr>
<td>Psychological</td>
<td>Tinnitus, dizziness, headache, paresthesia</td>
</tr>
<tr>
<td>Neurological</td>
<td>Dry mouth, hypertension</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Nausea, bloating, irritable bowel syndrome, reduced appetite</td>
</tr>
<tr>
<td>Psychological</td>
<td>Anxiety, insomnia, psychosis</td>
</tr>
</tbody>
</table>

Hey… what about these?

- Atypical Antipsychotics ....
  - Quetiapine

- Anticonvulsants ...
  - Lamotrigine
  - Gabapentin
Non-pharmaceutical therapy options

- Treatment for anxiety disorders = a participatory sport

- Non pharmaceutical options are viable options!
  - Psychotherapy
  - Meditation/Mindfulness
  - Exercise

Panic attacks are my cardio.
Non-pharmaceutical therapy options: CBT Psychotherapy

Cognitive Behavioral therapy

- Short term, skills focused treatment
- Goal = alter maladaptive emotional response by changing thoughts and behaviors
Non-pharmaceutical therapy options: CBT Psychotherapy

Exposure therapy
- Stimulus-Response change
- Systematic confrontation with a fear (thought or object)
- Reconditioned response
Non-pharmaceutical therapy options: Mindfulness/Meditation

Mindfulness meditation:
- Derived from Vipassana meditation in Buddhism
- Focus on present moment
- Encourage non-judgement
- Encourages detachment from destructive thoughts/feelings

Non-pharmaceutical therapy options: Mindfulness/Meditation

- Xu et al (2017) show that ten minutes of meditation per day:
  - Is preventative for “mind wandering”
  - Supports external focus, reduces internal focus

- Participation in an 8-week study showed significant decreases in anxiety levels of GAD patients (Evans 2016)

- Benefits of meditation on cardiovascular risk have been demonstrated

- Prevention of relapse of depressive disorders
Non-pharmaceutical therapy options: Mindfulness/Meditation with a guided apps

- [https://my.headspace.com/play/582](https://my.headspace.com/play/582)

[Headspace logo]

[Mindful logo]

[The Free Mindfulness Project logo]

[UCLA Mindful Awareness Research Center logo]

[Fragrant Heart logo]
Non-pharmaceutical therapy options: Acceptance & Commitment therapy

Acceptance & Commitment therapy
- Mindfulness + CBT
- RCT in 2012 demonstrated ACT = CBT for anxiety disorders (Arch et al)
Non-pharmaceutical therapy options: Exercise

- **Physical activity** – body movement by skeletal muscles that results in energy expenditure
- **Exercise** – subset of physical activity that is planned, structured, repetitive, and purposeful

“Well I walk all day at work”
Non-pharmaceutical therapy options: Exercise

- Endorphins: an endogenous opioid polypeptide compound

- In exercise, they are produced by pituitary and hypothalamus
  - Lead to opioid like sense of analgesia
  - Increase sense of wellbeing

- Exercise is known to:
  - ↑ Beta endorphin release = runners high
  - ↓ anxiety sensitivity
  - ↓ sympathetic nervous system and HPA axis reactivity
Non-pharmaceutical therapy options: Exercise
Non-pharmaceutical therapy options: Exercise

2017 meta-analysis:
- “exercise should be considered an evidenced-based option for anxiety symptoms among people with anxiety/stress related disorders” (Stubbs et al)

RCT in 2017
- found exercise beneficial in anxiety patients to help with smoking cessation (Smits et al)
Non-pharmaceutical therapy options: Exercise

- One population based study found “regular exercise is cross-sectionally associated with lower neuroticism, anxiety and depression” (Moor et al, 2006)

- Several studies indicate 70-90% max HR for 20 min 3x per week decreases anxiety sensitivity
  - Most substantial reduction is 90 min after activity
Thank you!
DSM V Diagnostic Criteria: Generalized Anxiety Disorder

- **Excessive anxiety and worry** (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
- The individual finds it **difficult to control the worry**.
- The anxiety and worry are **associated with three (or more) of the following six symptoms** (with at least some symptoms having been present for more days than not for the past 6 months):
  - Restlessness, feeling keyed up or on edge
  - Being easily fatigued.
  - Difficulty concentrating or mind going blank
  - Irritability
  - Muscle tension
  - Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
- The anxiety, worry, or physical symptoms **cause clinically significant distress or impairment** in social, occupational, or other important areas of functioning.
- The disturbance is **not attributable to the physiological effects of a substance** (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
- The disturbance is **not better explained by another medical disorder** (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).
DSM V Diagnostic Criteria: Social Anxiety Disorder (Social Phobia)

A. A marked and persistent fear of one or more social situations in which the person is exposed to unfamiliar people or to possible scrutiny by others.

B. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing.

C. The social situations almost always provoke fear or anxiety

D. The feared social situations are avoided or else are endured with intense anxiety or distress.

E. The fear or anxiety is out of proportion to the actual threat posed by the social situation and to the sociocultural context.

F. The fear, anxiety or avoidance is persistent, typically lasting six months or more.

G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The fear, anxiety or avoidance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition

I. The fear, anxiety or avoidance is and is not better accounted for by another mental disorder (e.g., panic disorder with or without agoraphobia, separation anxiety disorder, body dysmorphic disorder, a pervasive developmental disorder, or schizoid personality disorder).

J. If a general medical condition or another mental disorder is present, the fear in Criterion A is unrelated to it (e.g., the fear is not of stuttering, trembling in Parkinson's disease, or exhibiting abnormal eating behavior in anorexia nervosa or bulimia nervosa).

K. Specify if performance only (fear of speaking in public)
DSM V Diagnostic Criteria: Panic Disorder

- Recurrent unexpected panic attacks.

A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four (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, light-headed or faint
- Chills or heat sensations
- Paresthesia
- Derealization (feelings of unreality) or depersonalization (detached from oneself)
- Fear of losing control or going crazy
- Fear of dying

**Note:** The abrupt surge can occur from a calm state or an anxious state

**Note:** Culture-specific symptoms (e.g., tinnitus, neck soreness, headache, uncontrollable screaming or crying) may be seen. Such symptoms should not count as one of the four required symptoms.
DSM V Diagnostic Criteria: Panic Disorder (continued)

- At least one of the attacks has been followed by 1 month (or more) of one or both of the following:
  - Persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, “going crazy”).
  - A significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).

- The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism, cardiopulmonary disorders).

- The disturbance is not better explained by another mental disorder (e.g., the panic attacks do not occur only in response to feared social situations, as in social anxiety disorder; in response to circumscribed phobic objects or situations, as in specific phobia; in response to obsessions, as in obsessive-compulsive disorder; in response to reminders of traumatic events, as in posttraumatic stress disorder; or in response to separation from attachment figures, as in separation anxiety disorder).
DSM V Diagnostic Criteria: Specific Phobia

- Marked **fear or anxiety about a specific object or situation** (in children the fear or anxiety may be expressed by crying, tantrums, freezing, or clinging)
- The phobic object or situation almost always **provokes immediate fear or anxiety**
- The phobic **object or situation is actively avoided** or endured with intense fear or anxiety
- The **fear or anxiety is out of proportion to the actual danger** posed by the specific object or situation and to the sociocultural context
- The fear, anxiety or avoidance is persistent, typically lasting for **6 months or more**
- The fear, anxiety, or avoidance **causes clinically significant distress or impairment** in social, occupational, or other important areas of functioning
- The disturbance is **not better explained by the symptoms of another mental disorder**, including fear, anxiety, and avoidance of situations associated with panic-like symptoms or other incapacitating symptoms (as in agoraphobia); objects or situations related to obsessions (as in OCD); reminders of traumatic events (as in PTSD); separation from home or attachment figures (as in SAD); or social situations (as in social anxiety disorder)

**Specify**: Animal, natural environment, blood-injection-injury, situational, or other
DSM V Diagnostic Criteria: Obsessive-Compulsive disorder

A. Presence of obsessions, compulsions, or both:

- **Obsessions** are defined by:
  1. Recurrent and persistent thoughts, urges or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.
  2. The individual attempts to ignore or suppress such thoughts, urges, or images or tries to neutralize them with some other thought or action (i.e. by performing a compulsion).

- **Compulsions** are defined by:
  1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.
  2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.
B. The *obsessions or compulsions are time-consuming* (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The obsessive-compulsive symptoms are *not attributable to the physiological effects of a substance* or another medical condition

D. The disturbance is *not better explained by the symptoms of another mental disorder*


Citations


Citations


Citations