

# Anxiety Disorders and their Treatment

Psychiatry Clerkship Lecture

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# Objectives

- Overview of Anxiety Disorders
  - Case based
- Treatment of Anxiety
  - Pharmacotherapy
    - Benzodiazepines
    - SSRIs
    - Beta-blockers
    - Buspirone
  - Psychotherapy
    - Cognitive and Behavioral Therapies
- Board Review Questions

# Case 1

- 20 yo single female college student presents to the emergency room. Out of the blue, she experienced the onset of shortness of breath, palpitations, sweating, nausea, dizziness, and the fear that she was going to die. These symptoms developed and then resolved over a period of 15 minutes. She reports having 2 similar episodes in the past, but this one was “much worse.”

# Differential Diagnosis

## *Medical Conditions:*

- Arrhythmia
- Hypoglycemia
- Hyperthyroidism
- Asthma
- Hyperventilation
- Anaphylaxis
- Pulmonary embolus
- Myocardial infarction
- Pheochromocytoma
- Carcinoid syndrome
- Seizures

## *Drug-induced States:*

- Intoxication:
  - Amphetamine
  - Anticholinergics
  - Marijuana
  - Hallucinogens
  - Cocaine
  - Theophylline
- Withdrawal:
  - Alcohol
  - Benzos
  - Opiates

# Medical Work-up of Panic

- For all patients:
  - Vitals, pulse ox
  - Laboratory Studies: Chem 7, CBC, Tox screen, TSH, LFTs, UA, Calcium
  - EKG
- Depending on presentation, additional work-up may be necessary:
  - Chest x-ray
  - Stress test
  - D-dimer
  - Urine catecholamines
  - Cardiac enzymes
  - MRI of brain or EEG
  - ABG

# Panic Attacks

- A discrete period of intense fear or discomfort, with at least 4 of the following symptoms developed abruptly and reaching a peak within 10 minutes:

Palpitations	Dizziness or light-headed
Sweating	Derealization or depersonalization
Trembling	Fear of losing control or going crazy
Short of breath	Paresthesias
Chest pain or discomfort	Chills or hot flashes
Nausea / abdominal distress	

# Case 1 (continued)

- The medical work-up is negative and the patient continues to experience these episodes. She admits that she is under a lot of stress at school and is anxious about her upcoming exams. These episodes are becoming more frequent. She has started skipping classes because she is afraid that she will experience an episode while in class.

# Panic Disorder

## *DSM-IV-TR Criteria*

- A. Recurrent, unexpected panic attacks
- B. At least one attack has been followed by at least 1 month of:
  - Persistent concern about having additional panic attacks
  - Worry about the implications of the attack or its consequences (“going crazy”)
  - Significant change in behavior related to the attacks



# Panic disorder

Panic attack



Anticipatory Anxiety



Phobic Avoidance

# Panic Disorder - Neurobiology

- Autonomic Nervous System:
  - Increased sympathetic tone
  - Adapts more slowly to repeated stimuli
  - Responds excessively to moderate stimuli
- Central Nervous System:
  - Focus on the brainstem
    - Locus ceruleus of the pons (noradrenergic system)
  - Limbic system
    - Role in anticipatory anxiety
  - Prefrontal Cortex
    - Role in phobic avoidance

# Panic Disorder

- Epidemiology:
  - Lifetime Prevalence 1.5-5%
  - Women to Men: 2 to 1
  - Age of onset typically 20s
  - Most common co-morbid disorders: MDD, social phobia, OCD
- Prognosis:
  - 30-40% symptom-free at long-term follow-up
  - 50% continue to have mild symptoms
  - 10-20% have significant symptoms

# Effective Treatments for Panic

- Benzodiazepines
- Antidepressants
  - SSRIs
  - SNRIs
  - Tricyclics
  - MAOIs
- Cognitive Behavioral Therapy

# Treatment of Panic Disorder

- Once good control of symptoms is achieved, pharmacologic treatment should continue for 8-12 months
- 30-90% of patients who have been successfully treated will have a relapse when medications are discontinued

# Treatment of Panic Disorder

- Psychotherapy is also an effective treatment, in particular cognitive and behavioral therapies:
  - Cognitive therapy
    - Addresses the catastrophic beliefs of panic, and provides information about panic disorder
  - Behavioral therapies
    - Applied relaxation
    - Respiratory training
    - In vivo exposure to the feared stimulus

# Case 2

- A 40 yo man saw the September 11, 2001, terrorist attack on TV and subsequently learned that his brother had died in the attack. Six months later, he presented to his PCP to request a sleep aid. Further questioning revealed he had frequent intrusive thoughts of the attack, nightmares, difficulty falling asleep, and poor concentration. He would turn off the television whenever there was news about the terrorist attacks and avoided talking with his wife about the event.

# Post-traumatic Stress Disorder (PTSD)

## *DSM-IV TR Diagnostic Criteria*

- A. The person has been exposed to a traumatic event in which:
- The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
  - The person's response involved intense fear, helplessness, or horror



# Post-traumatic Stress Disorder (PTSD)

## B. Three or more **dissociative symptoms**

- “in a daze”, derealization, depersonalization, dissociative amnesia (can’t recall part of the event)

## C. Persistently **re-experiencing** the event

- Recurrent images, flashbacks, nightmares

## D. **Avoidance** of stimuli that recall the trauma

- Avoidance of conversations, places, people

## E. Increased anxiety or **arousal**

- Difficulty sleeping, poor concentration, irritability, hypervigilance, motor restlessness

# PTSD

- Epidemiology:

- Lifetime Prevalence of PTSD 8%
- Women > Men
  - But lifetime prevalence of trauma is more common in men
- Most prevalent in young adults
- Most common comorbid disorders are depression and substance abuse
- Most important risk factor: severity, duration, proximity of a person's exposure

# PTSD

- Course:
  - May begin at any time, usually begins within 3 months of trauma
  - With treatment, >50% achieve complete recovery within 3 months
- Symptom reactivation may occur with reminders of the original trauma
- Prognosis (Untreated):
  - 30% recover
  - 40% continue to have mild symptoms
  - 20% continue to have moderate symptoms
  - 10% have the same severity of symptoms or their symptoms become worse

# PTSD - Neurobiology

- Neurobiology:
  - Smaller hippocampi compared to controls
- Noradrenergic system:
  - Increased urine catecholamine concentrations in soldiers with PTSD and sexually abused girls
  - Flashbacks after administration of yohimbine (alpha-2-adrenergic antagonist)
- Opioid system:
  - Low plasma beta-endorphin concentrations
- HPA Axis:
  - Low plasma and urinary free cortisol levels
  - Enhanced suppression of cortisol by low-dose dexamethasone
  - Suggests hyperregulation of HPA Axis
  - These findings are specific to patients with PTSD, not just patients who have been exposed to a trauma

# PTSD – Treatment

- Pharmacotherapy
  - SSRIs are considered first-line
  - Tricyclics are also effective, often used as second-line
  - Prazosin (alpha1-blocker) is used in treatment of nightmares associated with PTSD
- Psychotherapy – 2 different approaches:
  - Exposure therapy – focus on desensitization to the traumatic event
  - Stress management – focuses on relaxation techniques and coping with stress

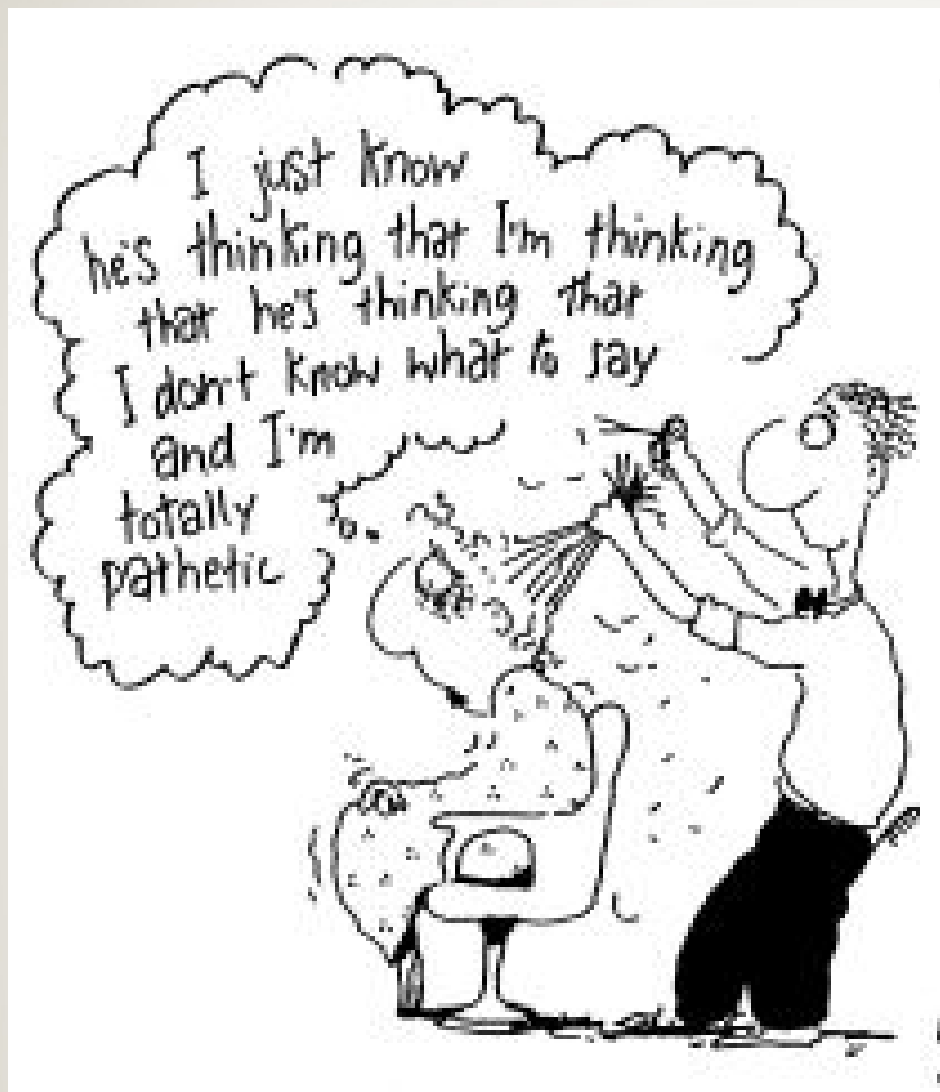
# Case 3

- The patient is a 30 yo businessman who comes to see you for “stage fright.” He has recently been promoted in his job and will now have to give public speeches a couple of times a year. He has always been afraid of speaking in public. Before giving a speech, he invariably develops palpitations, sweating, shortness of breath, and concerns that he is going to die or go crazy.

# Social Phobia

## *DSM-IV-TR Criteria*

- A marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or possible scrutiny by others.
- Exposure to the feared social stimulus almost invariably provokes anxiety
- The person recognizes the fear as excessive or unreasonable
- The feared social or performance situations are avoided or else endured with intense anxiety or distress





# Social Phobia

- “Generalized” Social Phobia:
  - subtype of social phobia in which the fears are present in most social situations
- “Specific” Social Phobia:
  - Writing, eating, speaking in public, etc.

# Social Phobia

- Epidemiology:
  - Lifetime Prevalence 3-13%
  - Women > Men
  - Comorbidity: other anxiety disorders, mood disorder, substance use disorders, and Avoidant PD
- Course:
  - Peak age of onset: teens
  - Generally lifelong, but may attenuate in adulthood

# Social Phobia – Treatment

- Medications:
  - SSRIs – generally considered first-line agents for generalized social phobia
  - SNRIs
  - Buspirone
  - Benzos
  - Beta blockers – used as PRN shortly before performance in social setting
- Psychotherapy – usually a combination of behavioral and cognitive techniques

# Case 3, Cont.

- Upon further questioning, the patient tells you that he is also very self-conscious of writing in public because he fears that he will make a mistake. He rarely uses public restrooms because he is often unable to urinate if other people are in the restroom. He also is “deathly afraid of flying” and refuses to fly even though travel is a requirement of his job.

# Specific Phobia

## Diagnostic Criteria:

- Marked unreasonable fear associated with specific object or situation
- Exposure to phobic stimulus provokes anxiety response
- Person recognizes that the fear is excessive or unreasonable
- Interferes with normal social or occupational functioning

## Different types of specific phobias:

1. Animal Type
2. Natural Environment Type (storms, heights)
3. Blood/Injection/Injury Type
4. Situational Type (flying, elevators)
5. Other (choking, clowns)

# Specific Phobia

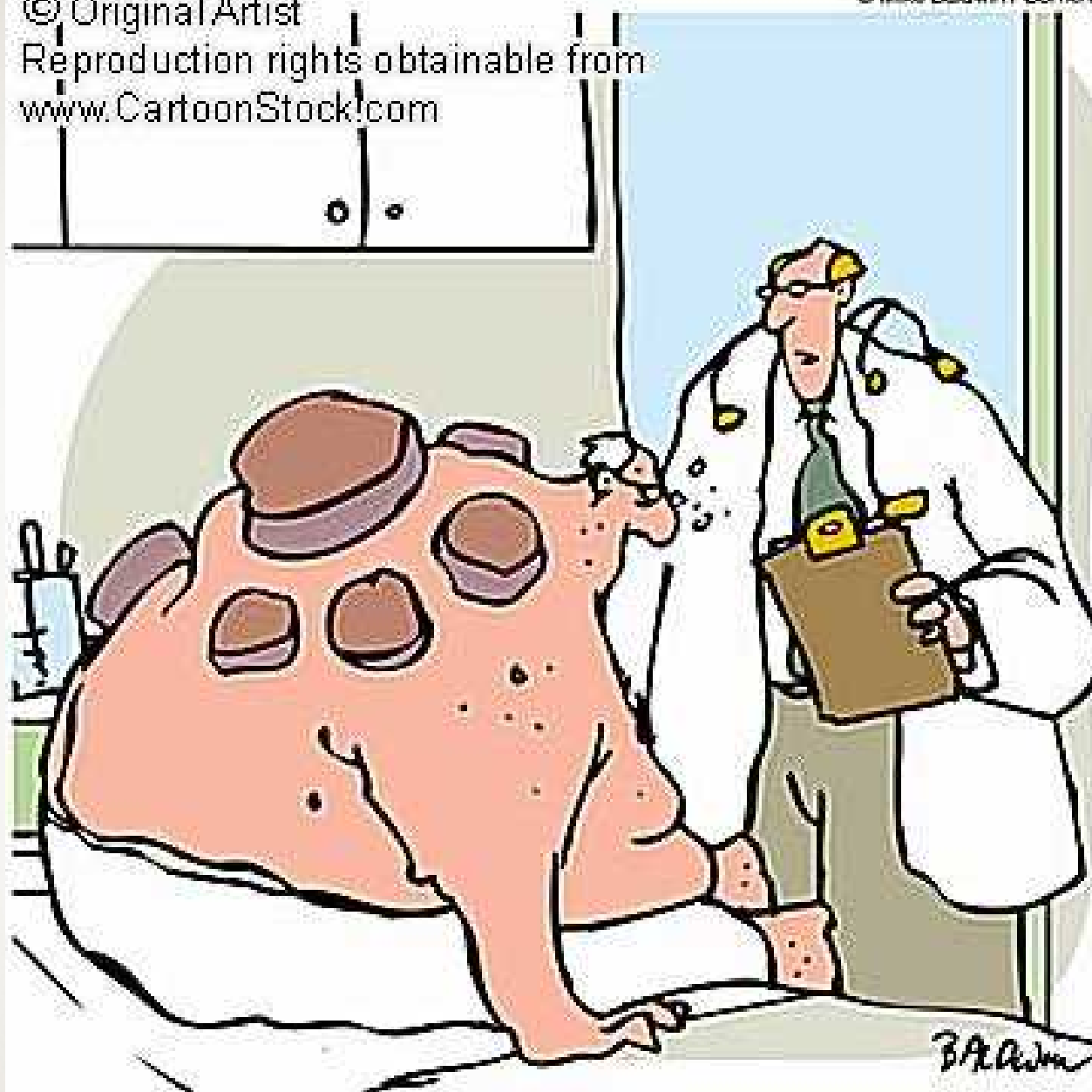
- Epidemiology
  - Lifetime Prevalence 11%
  - Women to Men = 2:1
  - Age of onset:
    - Animal, Natural, Blood/Injection/Injury -- 5 to 9 years
    - Situational -- typically 20's
- Treatment
  - Exposure Therapy (aka exposure response prevention/ERP) is primary treatment
    - Specific type of behavioral therapy
    - Goal is to desensitize patients through self-paced exposures to the phobic stimulus
    - Patients learn techniques to deal with anxiety
  - Beta blockers may also be useful, especially when the phobic stimulus triggers a panic attack

# Case 4

- Pt is a 30 yo trial attorney who, for the past year, has noted increased worrying about her upcoming trials. She also spends time worrying about her physical health, her children's health, and her children's performance in school. She has been feeling increasingly fatigued, irritable, and tense, and has difficulty getting to sleep at night because of her worrying.

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“Relax, they’re just worry warts.”



# Generalized Anxiety Disorder (GAD)

## *DSM-IV-TR Criteria*

- Excessive worry and anxiety more days than not for at least 6 months
- Person finds it difficult to control the worry
- Three or more of:
  - Restless, keyed-up, on edge
  - Easily fatigued
  - Difficulty concentrating
  - Irritability
  - Muscle Tension
  - Sleep Disturbance

# Generalized Anxiety Disorder (GAD)

- Epidemiology
  - Lifetime prevalence 5%
  - Women to Men: 2 to 1
  - Age of onset usually 20s to 30s
  - Most common co-morbid disorders: mood disorder, panic disorder
  - For only 20%, GAD was the first-onset disorder or the only lifetime disorder

# GAD – Treatment

- Pharmacotherapy
  - Benzos – can be prescribed on an as-needed basis, or for a short period of time at the initiation of treatment until SSRIs/psychosocial interventions become effective
  - SSRIs / SNRIs
  - Buspirone – more effective at treating the cognitive symptoms than the somatic symptoms
- Psychotherapy
  - Cognitive-behavioral techniques

# Case 5

- Pt is a 10 yo male who has become increasingly anxious over the previous six months, becoming significantly preoccupied with his morning routine. In order to leave home for school, he must watch his goldfish swim “up, then down and to the left...or something bad will happen.” He is normally an “A” student, but his grades have declined despite extra time spent on homework. He realizes that his thoughts are excessive; however, he can not stop for fear that his family members will die if he does not perform his routines.

# Obsessive-Compulsive Disorder (OCD)

- Obsessions

- recurrent and persistent thoughts, impulses, or images that are experienced as intrusive and inappropriate and that cause marked anxiety or distress
- the thoughts, impulses, or images are not simply excessive worries about real-life problems
- the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action
- the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind

- *Common obsessions* (highest to lowest incidence):

- Contamination, pathological doubt, somatic, need for symmetry, aggressive, sexual
- 60% have multiple obsessions

# Obsessive-Compulsive Disorder (OCD)

- Compulsions

- repetitive behaviors or mental acts that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly
  - the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation but behaviors are not connected in a realistic way
- *Common compulsions*: checking, washing, counting, need to ask/confess, symmetry/precision, hoarding multiple
- At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable.
- The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal functioning

# Obsessive-Compulsive Disorder (OCD)

- **EPIDEMIOLOGY**

- The lifetime prevalence of OCD = 2-3%
- Child/adolescent prevalence = 1-2.3% (4th most common psychiatric diagnosis behind phobias, substance abuse, and MDD)
- There is similar epidemiology among diverse cultures
- In adults, male and female prevalence is the same. In children and adolescents, males are more likely than females to be affected.
- Mean age of onset approximately 20 (men earlier than women)

- **COMORBIDITY:** 67% of patients have lifetime prevalence of MDD; 5-7% incidence of Tourette's disorder; 20-30% incidence of tic disorder

# Obsessive-Compulsive Disorder (OCD)

- **TREATMENT – combination of CBT and medication**

- Medications as treatment include:
  - SSRI
  - TCAs, in particular clomipramine (Anafranil) – has potent serotonin reuptake inhibition.
  - Other medications like gabapentin, lamotrigine, and atypical antipsychotics have also been found to be useful as adjuncts in the treatment of OCD.
- Psychosurgery or Deep Brain Stimulation – focus on cingulate gyrus

- **COURSE AND PROGNOSIS**

- 50% of patients have sudden onset, usually occurring after stressful event
- usual delay of 5-10 years before seeking psychiatric attention (due to secretive nature of disorder)
- 20-30% have significant improvement, 40-50% moderate, and 20-40% remain stable or worsen

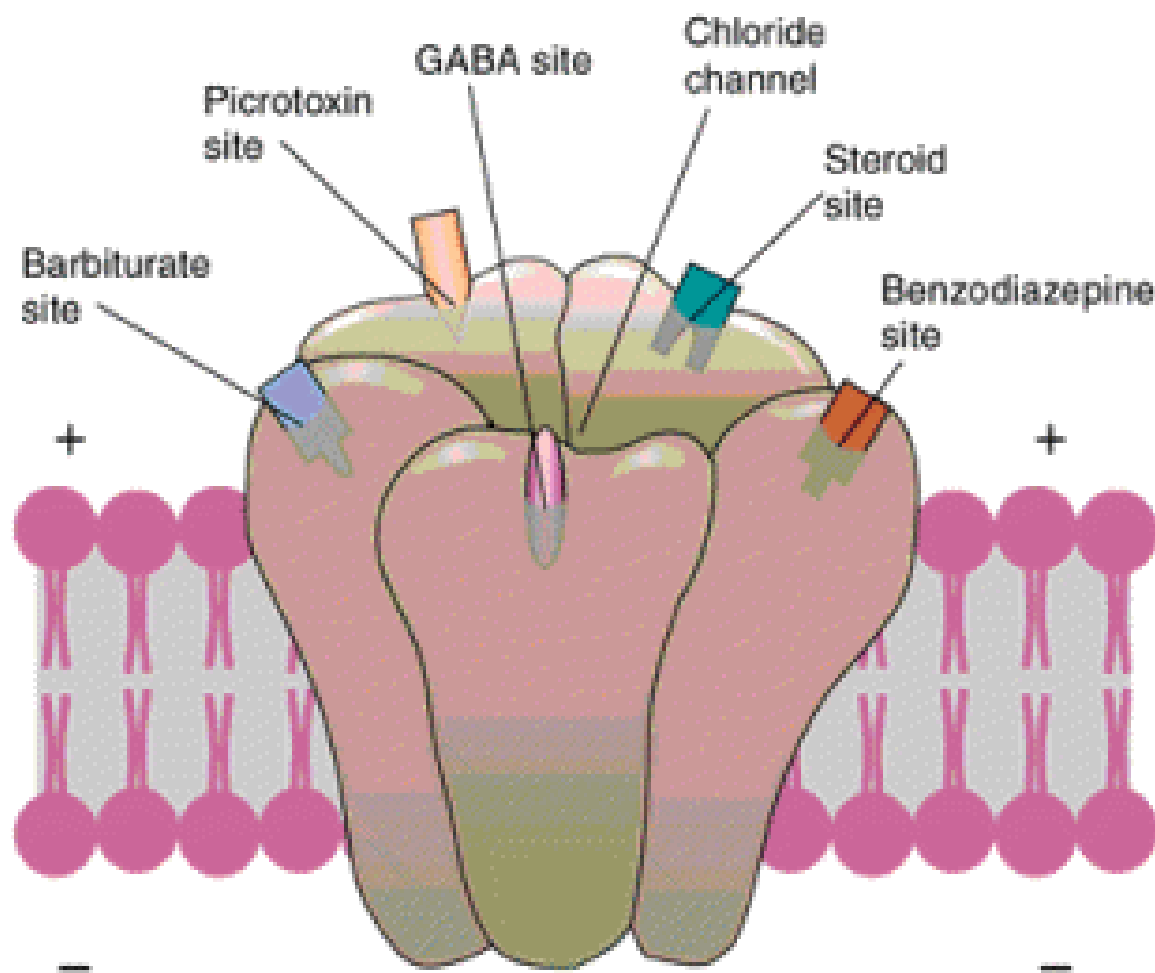


# Pharmacologic Treatment of Anxiety

# Benzodiazepines

- Classified as sedative-hypnotics
- Drug of choice for managing acute anxiety
- Mechanism of action:
  - Bind to specific receptors in the gamma aminobutyric acid (GABA<sub>A</sub>) receptor complex, leading to enhanced binding of this inhibitory neurotransmitter
  - Result is decreased rates of neuronal and muscle firing
- Due to wide tissue distribution, benzos have multiple effects:
  - Sedation / anxiolytic
  - Muscle relaxant
  - Anticonvulsant

► Schematic Illustration of a GABA<sub>A</sub> Receptor, with Its Binding Sites



# Benzodiazepines

- Common side effects:
  - Sedation, dizziness, ataxia, cognitive slowing
- Benzodiazepine tolerance and withdrawal:
  - When used short-term (1-2 wks) at moderate dosages, tolerance and withdrawal usually do not develop
  - Long-term use of benzos → withdrawal syndrome
    - More common with benzo with short half-lives (alprazolam)
    - To reduce risk for withdrawal symptoms, taper slowly at rate of 25% per week
    - Switch to a longer half-life benzo (e.g. alprazolam to clonazepam) or use of carbamazepine may alleviate withdrawal symptoms

# Benzodiazepines

*Benzodiazepines differ in their absorption rates, lipid solubility, metabolism and half-lives*

<u>Benzodiazepine</u>	<u>Half-life</u>
Chlordiazepoxide (Librium)	> 100 hours
Diazepam (Valium)	100 hours
Clonazepam (Klonopin)	20-50 hours
Lorazepam (Ativan)	15 hours
Alprazolam (Xanax)	12 hours
Midazolam (Versed)	2 hours

# Benzodiazepines

- Quickest onset of action:
  - Diazepam
  - Lorazepam
  - Alprazolam
- Reliable absorption IM:
  - Lorazepam
  - Midazolam
- Most benzos are metabolized by liver
  - P450 3A3/4 isoenzyme
  - Exceptions are temazepam, lorazepam and oxazepam → use these in patients who have liver dysfunction

# Benzodiazepines – Dose Equivalents

Lorazepam – 1 mg

Clonazepam – 0.5 mg

Diazepam – 5 mg

Alprazolam – 0.25 mg

Chlordiazepoxide – 10 mg

Temazepam – 5 mg

# SSRIs and Other Antidepressants



# SSRIs

- Fluoxetine (Prozac)
  - Longest half-life
  - First drug of this class
  - Many P450 interactions
  - Dose 20-80 mg/day
- Sertraline (Zoloft)
  - SDRI at higher doses
  - Safe in breastfeeding
  - Dose 50-200 mg/day
- Paroxetine (Paxil)
  - Most anticholinergic
  - More weight gain than others
  - Shortest half-life
  - Dose 20-50 mg/day
  - Teratogen: cardiac defects
- Citalopram (Celexa)
  - Lowest interactions
  - Escitalopram (Lexapro) is enantiomer (and more \$\$)
  - Dose 20-60 mg/day
- Fluvoxamine (Luvox)
  - Primary for Tx of OCD
  - P450 interactions
  - 100-300 mg/day

Other Medications:

Buspirone

Beta-blockers

# Buspirone

- Anxiolytic, also used as adjunctive treatment for depression
- Serotonin 1A receptor partial agonist
- Onset of action typically 2-4 weeks
- Usual dose is 20-30 mg/day in divided doses BID
- Side effects: dizziness, headache, sedation or excitement
- Does not appear to cause dependence or withdrawal

# Beta Blockers

- Useful for treatment of social phobia, primarily performance type
  - Propranolol or atenolol are most frequently used
  - Administered ½ hour before performance
  - Blocks sympathetic drive, preventing outward signs of anxiety such as palpitations and sweating
- Other uses in psychiatry:
  - Akathesia
  - Lithium-induced tremor
  - Alcohol withdrawal

# Psychotherapeutic Treatment of Anxiety Disorders:

## **Cognitive Behavioral Techniques**

# Behavioral Therapy

- Applications of the principles of learning theory (classical conditioning, operant conditioning, etc.)
- Systematic Desensitization:
  - Patients attain a state of complete relaxation and are then exposed to the stimulus that elicits the anxiety response
  - Progress through a graded list or hierarchy of anxiety-provoking scenes while in a deeply relaxed state
  - Uses imagery (not actual experiences)

# Behavioral Therapy

- Therapeutic graded exposure:
  - Relaxation training is not involved
  - Treatment is carried out in real-life context
  - Individual is brought in contact with the feared stimulus in a graded list or hierarchy
- Flooding
  - Similar to graded exposure, but there is not hierarchy
  - Patient is exposed to the feared stimulus
  - Clinician does not allow patient to escape the stimulus
  - Patient remains in the situation until calm and feel a sense of mastery

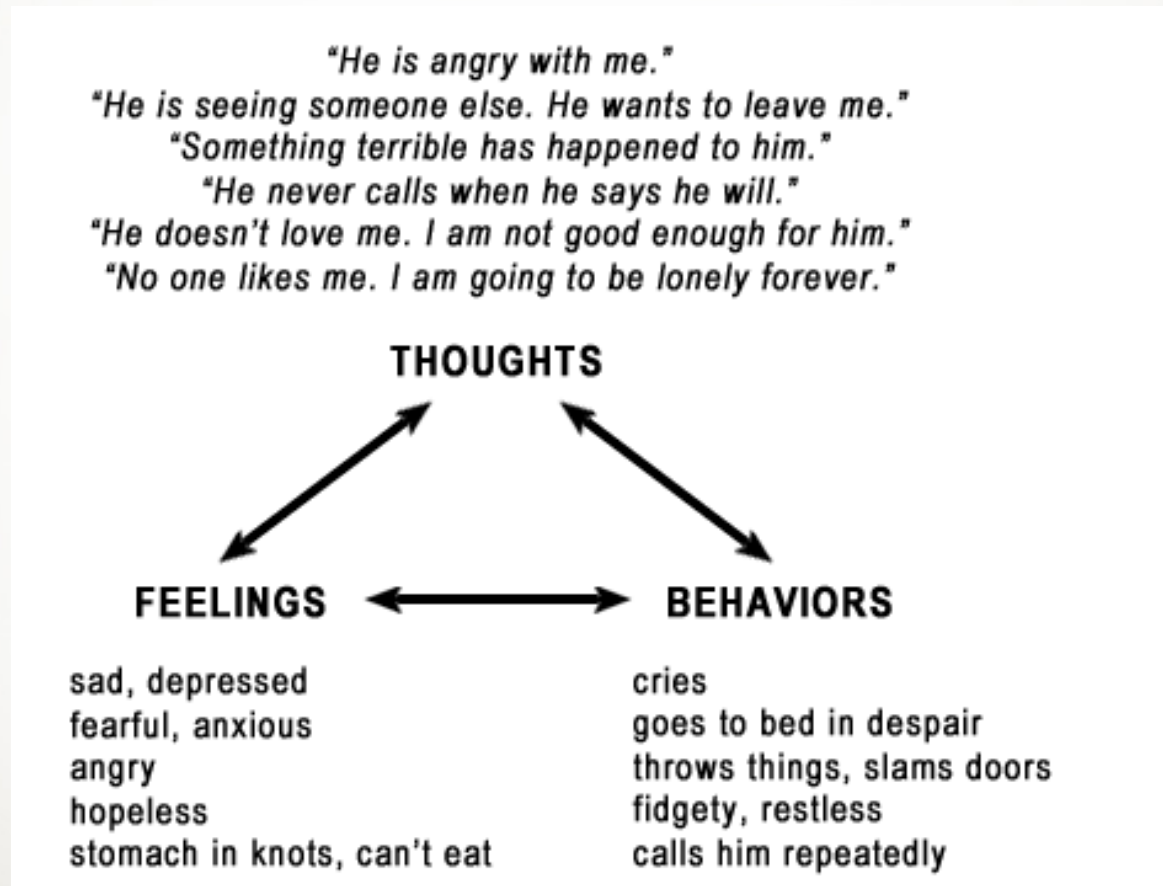
# Cognitive Therapy

- Based on the idea that an individual's affect and behavior are based on cognitions
- Cognitions (verbal or pictorial ideas available to the consciousness) are based on assumptions (schemas developed by previous experiences)
- Cognitive distortions are cognitions that intervene between external events and a person's emotional reaction to the event
- Cognitive therapy is a short-term, structured therapy that is oriented toward current problems and their resolutions



# History of CBT (cont.)

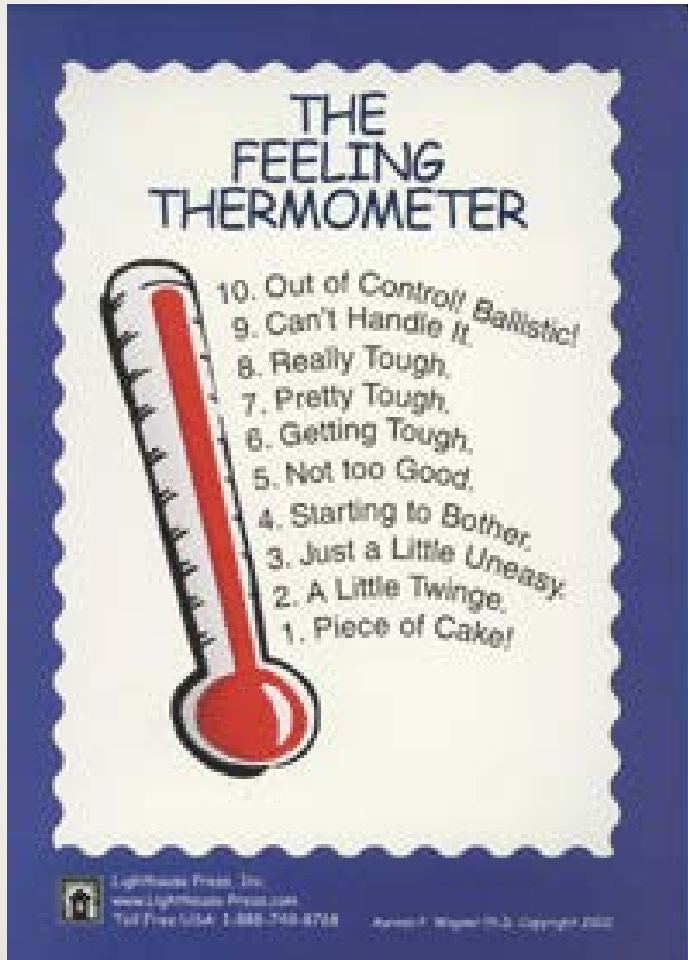
- Commonly used CBT model:



# Session Structure

- Goals for First Sessions/Intake:
  - Establish rapport and trust
  - Socialize patient (and family) to CBT-based treatment
  - Assess patient and educate the patient about his/her disorder, the CBT model, and the therapy process
  - Normalize difficulties and instill hope
  - Review therapy expectations
  - Gather any additional information for case conceptualization
  - Develop problem list/hierarchy

# “Feelings Thermometer”



- Provides a method of creating a problem list or hierarchy for treatment
- I often let patients create their own thermometer and label items/severity in their own words
- Will adapt/create new thermometer as treatment progresses

# SUMMARY

- Anxiety disorders
  - Know the DSM-IV criteria
  - High prevalence rate
  - Usually women > men, onset young adulthood
  - Variety of neurobiological theories
- Treatments for all tend to be similar
  - Benzos can be used short-term
  - Antidepressants as a class are effective
    - Agents that target serotonin are most effective
  - Combination of cognitive and behavioral therapies are used in psychotherapy

# Boards Questions

# Question

1. The following manifestations of panic attacks help differentiate panic attacks from partial seizures:
- A. They occur “out of the blue”
  - B. They present with intense fear, perceptual distortion, and dissociative symptoms.
  - C. They respond to benzodiazepines.
  - D. They last 10-20 minutes with memory of event intact.

# Question

2. A man presents to ED pale with perioral cyanosis and shallow respirations of 3-5/min. He is unresponsive. A friend reports that the patient “may have taken something to relax”. The drug most likely to treat the acute respiratory depression:

- A. Flumazenil
- B. Clonidine
- C. Pentazocine
- D. Amitriptyline

# Question

3. Which of the following comorbid conditions is most commonly seen in men with PTSD?

- A. Agoraphobia
- B. Panic Disorder
- C. Major Depressive Disorder
- D. Alcohol Abuse/Dependence
- E. Generalized Anxiety Disorder



# Question

4. Which of the following is the most potent inhibitor of the norepinephrine transporter?
- A. Citalopram
  - B. Fluoxetine
  - C. Sertraline
  - D. Venlafaxine

# Question

5. Which of the following medications is least likely to produce sexual side effects?

- A. Citalopram
- B. Bupropion
- C. Venlafaxine
- D. Fluoxetine

# Question

6. An 18 yo male presents to the ED with sudden onset of anxiety. He had the sudden onset of a pounding heartbeat, SOB, and chest pain. On exam, HR is 200 and BP 90/60. Pt is instructed to hold his breath and bear down. After doing this, pt feels much improved. What did he most likely have?
- A. Panic Attack
  - B. Carcinoid Syndrome
  - C. Paroxysmal atrial tachycardia
  - D. Pulmonary embolus

# Question

7. When compared with younger adults, anxiety disorders in adults over age 65 have:
- A. Higher incidence
  - B. Greater prevalence
  - C. Less comorbidity with alcohol abuse
  - D. Less association with depressive symptoms

# Question

8. The presence of which of the following disorders puts a child at greatest risk for developing panic disorder as an adult?
- A. Simple phobia
  - B. Separation anxiety disorder
  - C. Major depression
  - D. Attention-deficit hyperactivity disorder

# Question

9. 20 yo patient presents to his doctor worried that he has contracted an infectious disease. He counts to 100 repeatedly to distract him from this worry. He has no symptoms or medical problems, and is not abusing substances. Which of the following regions in his brain is likely to show increased activity on PET scan?
- A. Caudate
  - B. Hippocampus
  - C. Thalamus
  - D. Cerebellum

# Question

10. A 40 yo patient experienced delirium, tremor, diaphoresis, rigidity, hyperpyrexia, and myoclonus after switching to clomipramine from phenelzine (an MAOI). He most likely has:
- A. Serotonin Syndrome
  - B. Serotonin Discontinuation syndrome
  - C. Neuroleptic malignant syndrome
  - D. MAOI-tyramine reaction

# Answers

1. D
2. A
3. D
4. D
5. B
6. C
7. C
8. B
9. A
10. A