

“Therapeutic Management of Anxiety Disorders”

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Objectives:

- Describe different types of anxiety disorders.
- Compare and contrast signs and symptoms of different types of anxiety disorders.
- Discuss treatment options for anxiety disorders.

Epidemiology of Anxiety Disorders

- The National Comorbidity Study reported that one in four persons met the diagnostic criteria for at least one anxiety disorder
- Anxiety disorders have a 12-month prevalence rate of 17.7 percent.
- Women have a lifetime prevalence of 30.5 percent versus 19.2 percent prevalence in men.
- Prevalence of anxiety disorders decreases with higher socioeconomic status.

Epidemiology of Anxiety Disorders

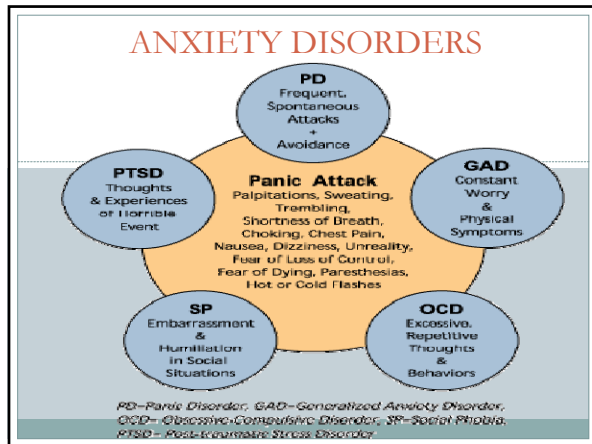
- Estimated at approximately 25%* (lifetime prevalence)
 - Approximately 13.3% are Social phobias
 - Approximately 11.3% are Simple Phobias
 - Approximately 3.5% are Panic Disorder
 - Approximately 2.5% are OCD
 - Approximately 5.1% are GAD
- Women > Men
- Mostly untreated leading to high utilization of the healthcare system

Types of Anxiety Disorders Based on the DSM-IV-TR

- Generalized Anxiety Disorder
- Social Anxiety
- Post Traumatic Stress Disorder
- Obsessive Compulsive Disorder
- Phobic Disorders
- Panic Disorder with or without agoraphobia
- Atypical Anxiety Disorder

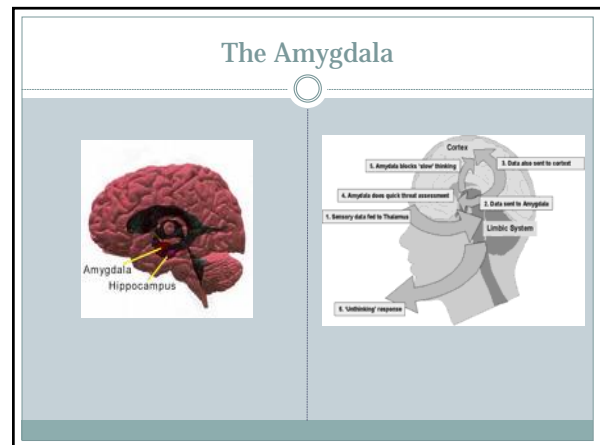
Anxiety Disorders listed in the DSM-IV-TR

- | | |
|---|---|
| ☐ Panic disorder with agoraphobia | ☐ Posttraumatic Stress Disorder |
| ☐ Panic disorder without agoraphobia | ☐ Acute Stress Disorder |
| ☐ Agoraphobia without history of panic disorder | ☐ Generalized Anxiety Disorder |
| ☐ Specific phobia | ☐ Anxiety Disorder due to a general medical condition |
| ☐ Social phobia | ☐ Substance-induced anxiety disorder |
| ☐ Obsessive-Compulsive Disorder | ☐ Anxiety Disorder NOS |



- ## Etiological Factors for Anxiety Disorders
- Primary Anxiety Disorders
 - Biological pathology-neurotransmitter related
 - Secondary Anxiety Disorders
 - Substance-induced anxiety
 - Medical conditions
 - Social/environmental Stressors
 - Psychiatric Illnesses

- ## Biological Theories of Anxiety Disorders
- ▣ Autonomic Nervous System Stimulation
 - Cardiovascular (i.e., tachycardia)
 - Muscular (i.e., headache)
 - Gastrointestinal (i.e., diarrhea)
 - Respiratory (i.e., tachypnea)
 - ▣ Neurotransmitter Association
 - Norepinephrine
 - Serotonin
 - GABA
 - ▣ Brain-imaging studies
 - ▣ Genetic studies
 - ▣ Neuroanatomical Considerations



- ## Peripheral Manifestations of Anxiety
- Diarrhea
 - Dizziness, light-headedness
 - Hyperhidrosis
 - Hyperreflexia
 - Palpitations
 - Pupillary mydriasis
 - Restlessness
 - Syncope
 - Tachycardia
 - Tingling in the extremities
 - Tremors
 - Upset stomach
 - Urinary Frequency

- ## Differential Diagnosis for Anxiety Disorders
- Cardiovascular/Respiratory Disorders
 - Arrhythmias
 - COPD
 - Hypertension
 - Angina
 - Myocardial Infarctio
 - Endocrine system
 - Hyperthyroidism
 - Hypothyroidism
 - Hypoglycemia
 - Pheochromocytoma
 - Gastrointestinal
 - Colitis
 - Irritable Bowel Syndrome
 - Peptic ulcers
 - Ulcerative colitis
 - Miscellaneous
 - Epilepsy
 - Migraine
 - Pain
 - Pernicious anemia
 - Porphyria

Medications Associated with Anxiety Symptoms

- **CNS Stimulants**
 - Albuterol
 - Amphetamines
 - Cocaine
 - Isoproterenol
 - Methylphenidate
 - Caffeine (NoDoz, Vivarin)
 - Ephedrine
 - Naphazoline
 - Oxymetazone
 - Phenylephrine
 - Pseudoephedrine
- **CNS Depressants**
 - Anxiolytics/sedatives
 - Ethanol
 - Narcotics (withdrawal)
- **Miscellaneous**
 - Anticholinergic toxicity
 - Baclofen
 - Digitalis toxicity
 - Dapsone
 - Cycloserin

Assessment Scales for Anxiety Disorders

- **HAM-A**
- **Scared Child Scale**
- **Fear Questionnaire**

Treatment Options for Anxiety Disorders

- **Psychotherapy**
- **Behavioral Therapy**
- **Pharmacotherapy**

Biological Pathophysiology of Anxiety Disorders

- **Abnormal functioning of neurotransmitters:**
 - Norepinephrine
 - Serotonin
 - Glutamate
 - Neuropeptides
 - γ -aminobutyric acid (GABA)

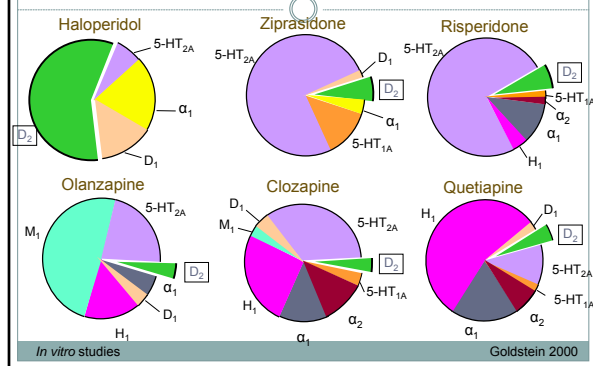
Novel Treatment Options for Managing Anxiety Disorders

- **Atypical Antipsychotics**
- **MDMA**
- **Pregabalin**
- **Others***

The Rationale for Using the Atypical Antipsychotics

- **Atypical Antipsychotics have traditionally been used as augmentation options for depression and anxiety.**
- **Atypical Antipsychotics can assist in improving the rates of remission.**
- **Atypical Antipsychotics are excellent in addressing certain aspects of mood disorders.**
- **Atypical Antipsychotics have impressive onsets of action for resolving anxiety disorders.**
- **Atypical Antipsychotics are not addicting.**

Receptor pharmacology: predominant D2 binding is a feature of typical antipsychotics



Rationale for MDMA in Anxiety Disorders

- MDMA binds and reverses monoamine transporters, resulting serotonin release seems to mediate most of the subjective effects.
- MDMA increases oxytocin release which enhances the encoding of positive social memories.
- MDMA increases norepinephrine and cortisol release.
- MDMA increases ventromedial prefrontal activity and decreases amygdala activity, which may improve emotional regulation and decrease avoidance

Anxiety Disorders



Generalized Anxiety Disorder

- Unrealistic or excessive anxiety or worry about 2 or more life circumstances for a period of six months or longer. Absence of any organic factors.
- Symptoms must be present in three domains: motor tension, autonomic hyperactivity, and vigilance or scanning.

Diagnostic Criteria for GAD

*Must have six of the following

Motor Tension	Autonomic Hyperactivity	Vigilance or Scanning
Trembling	Shortness of breath	Feeling keyed up or on edge
Muscle tension	Palpitations or tachycardia	Startling easy
Restlessness	Sweating or cold clammy hands	Difficulty concentrating
Easily fatigued	Dry mouth	Trouble falling asleep or staying asleep
	Dizziness or lightheadedness	Irritability
	Nausea, diarrhea, or GI distress	
	Hot or cold flashes	
	Frequent urination	
	Trouble swallowing	

Nonpharmacological Treatment for GAD

- Should be primary treatment option*
- Behavioral, supportive psychotherapy, group therapy, biofeedback, and other relaxation therapy

Pharmacotherapy Options for GAD

- **Pharmacotherapy**
 - Benzodiazepines
 - Buspirone
 - Venlafaxine
 - Certain Antidepressants
 - Beta Blockers
 - Antihistamines
- **Psychotherapy**
 - Cognitive Behavioral Therapy
- **Drugs of Choice**
 - SSRIs
 - TCAs
 - Buspirone
 - MAOIs
 - Effexor

Pharmacotherapy Options Used for GAD

Medication	FDA-Approval	Usual dosage range (mg/day)
Diphenhydramine	No	25-200
Hydroxyzine	Yes	50-400
Meprobamate	Yes	400-1600
Propranolol	No	80-160
Buspirone	Yes	15-60
Venlafaxine	Yes	25-375

Augmentation Options

- Risperidone
- Olanzapine
- Ziprasidone
- Quetiapine

Studies of Quetiapine XR in GAD

- **Khan et al 2008**
 - 10-wk, double-blind, placebo-controlled, randomized, parallel-group, N=951; Doses: 50-300mg
- **Chouinard et al 2008**
 - 10-wk, double-blind, placebo-controlled, randomized, parallel-group, active-controlled, N=873; Doses 50-150mg
- **Katzman et al 2008**
 - 52-wk, double-blind, placebo-controlled, randomized-withdrawal, parallel-group, N=433; Doses 50-150mg

Studies of Quetiapine XR in GAD

Study	Response Rates	Remission Rates
Khan et al 2008	50mg/d: 60.3* 150mg/d: 61.5* 300mg/d: 54.9 ^{ns} Placebo: 50.7	50mg/d: 36.1 ^{ns} 150mg/d: 37.2* 300mg/d: 28.6 ^{ns} Placebo: 27.6
Chouinard et al 2008	50mg/d: 62.6* 150mg/d: 70.8*** Paroxetine: 65.9*** Placebo: 52.1	50mg/d: 32.4 ^{ns} 150mg/d: 42.6** Paroxetine: 38.8* Placebo: 27.6
Katzman et al 2008	None	None

*p<0.05, **p<0.01, ***p<0.001, ^{ns}vs placebo,

Buspirone (Buspar®)

- Possesses no BZD or GABA complex activity, but has some dopaminergic activity
- Onset of action: 2-4 weeks
- Not intended for prn use
- No addiction potential
- Multiple dosing required
- More effective if used prior to BZDs
 - Due to lack of euphoriant effects
 - Does not have cross-tolerance with BZDs

Buspirone (Buspar®)

- **Drug Interactions**
 - Haloperidol and MAOIs
 - Fluoxetine & Paroxetine
 - *Supposedly no interaction with alcohol*
- **Adverse Reactions:** nausea, dysphoria, headache, weakness, dizziness, nervousness
 - May potentially cause gynecomastia, Galactorrhea, EPS

FDA-Approved Benzodiazepines Used for GAD

Medication	Approved Indications	Approved Dosage Range (mg/day)	Approved Equivalent Dose (mg)
Alprazolam	Anxiety, anxiety-depression, panic disorder	0.75-4	0.5
Chlordiazepoxide	Anxiety, Alcohol withdrawal, Pre-op sedation	25-200	10
Clorazepate	Anxiety, seizures.	7.5-90	75
Diazepam	Anxiety, alcohol withdrawal, muscle spasms, pre-op sedation, status epilepticus	2-40	5
Halazepam	Anxiety	20-160	20
Lorazepam	Anxiety	0.5-10	1
Oxazepam	Anxiety, anxiety-depression, alcohol withdrawal	30-120	15
Przepam	Anxiety	20-60	10

Drug Interactions for Benzodiazepines

- Alcohol
- Antacids
- Cimetidine
- Disulfiram
- Fluoxetine
- Isoniazid
- Omeprazole
- Oral Contraceptives
- Rifampin

Concerns with Use of Benzodiazepines

- Potential for psychological dependence
- Can cause anterograde amnesia
- Increases risks for falls
- Can impair swallowing
- Can cause terminal insomnia
- Can cause rebound insomnia
- Can worsen depressive disorders

Pregabalin for Generalized Anxiety Disorder

- Safe and effective at doses of 150mg/day or 600mg/day treating generalized anxiety disorder
- Double-blind, placebo-controlled trial
- As effective as benzodiazepines without withdrawal symptoms, making it a potentially good alternative

Am J Psych. 2003;2160:533-540.

Types of Symptoms of PTSD

*Must be present at least 1 month before a diagnosis can be made.

- An overwhelming traumatic event is **re-experienced**, resulting in feelings of fear, helplessness, or horror.
- This traumatic experience results in **avoidance of stimuli** that might provoke thoughts of the event and increased arousal (i.e. jumpiness, nervousness, irritability).
- The person may also experience a generalized **numbing of emotions** in order to control these intense thoughts.

Features of PTSD

- Acute PTSD may last up to three months
- Chronic PTSD persists longer than three months
- PTSD is often accompanied by other psychiatric disorders including, depression, substance abuse, and personality disorders

Additional Symptoms of PTSD

- ☐ Alienating yourself to prevent stressful situations
- ☐ Avoiding people and places that remind you of the trauma
- ☐ Panicking in social situations you cannot escape
- ☐ Hiding your feelings of anxiety and fear
- ☐ Smiling or laughing so others think you're happy
- ☐ Withdrawing from relationships with loved ones
- ☐ Struggling to fall asleep ... and stay asleep
- ☐ Reliving the trauma in dreams and flashbacks
- ☐ Suffering in your performance at work
- ☐ Drinking or abusing drugs to mask your problems
- ☐ Avoiding plans for a future you doubt you'll see
- ☐ Thinking about suicide
- ☐ Feeling like you're facing all of this alone

Screening for PTSD

If >2 questions are answered with "yes", the diagnosis is probable.

- **In your life have you ever had any experience that was so frightening, horrible or upsetting that in the past month, you:**
 - Have you had nightmares about it or thought about it when you did not want to? YES/NO
 - Tried hard not to think about it or went out of your way to avoid situations that reminded you of it? YES/NO
 - Were constantly on guard, watchful or easily startled? YES/NO
 - Felt numb or detached from others, activities, or your surroundings? YES/NO

Screening for Post Traumatic Events

- Serious accidents
- Natural disasters
- Physical attacks or assaults
- Sexual assaults
- Witnessing someone being badly hurt or killed
- Domestic violence or abuse
- Physical or emotional abuse as a child
- Being threatened with a weapon or held captive
- War (as a civilian or in the military)
- Torture or an act of terrorism
- Any other extremely stressful or upsetting event

Treatment of PTSD

- Patients receiving adequate treatment have an median recovery time of 36 months, as compared with 64 months in patients who are untreated.
- Psychotherapy
- Behavioral Therapy
- Pharmacotherapy
- The primary goal of chronic PTSD with co-morbid psychiatric conditions is treatment of symptoms in conjunction with psychotherapy.

FDA-Approved Therapies for PTSD

- Cognitive therapy
- Exposure therapy
- EMDR (Eye Movement Desensitization and Reprocessing)
- Pharmacotherapy*

Psychological First Aid

- **For recent trauma (within the first 2 weeks)**
 - Monitor mental state and stabilize if required.
 - Encourage re-engagement in routines and use of social supports.
 - Ensure basic needs are met (i.e., housing, safety)
 - Review in 1-2 weeks.

Specific Pharmacotherapies for PTSD

Treatment Options	Comments
Tricyclics Amitriptyline Imipramine	Studied for 8 weeks; consistently more effective than placebo
MAOIs Phenelzine	Effective with imipramine
SSRIs Fluoxetine Sertraline Paroxetine Fluvoxamine Escitalopram	Variable effects
SNRIs Venlafaxine	Beneficial in one patient

Specific Pharmacotherapies for PTSD

Treatment Options	Comments
Atypical antidepressants Nefazodone Mirtazepine Trazodone	Studies conducted b/w 1998-99; 12 wks. Effective in 50%; Small sample size; 8 wks
Anticonvulsants Carbamazepine Lamotrigine Vigabatrin Gabapentin Valproic acid	General improvement in hyperarousal symptoms, impulse control, & intrusive symptoms; small sample sizes
Sympathomimetics Clonidine Propranolol	Effective in children and adults
Lithium	Reduced anger and aggression
Bupirone	Three studies; small sample sizes
Cyproheptadine	Effective in insomnia and nightmares

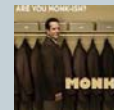
Efficacy of Atypical Antipsychotics in PTSD

Treatment Options	Comments
Olanzapine	Three studies; <8 wks.; effective adjunctively
Clozapine	Two studies; N= 72; effective adjunctively
Quetiapine	Four studies; N=146; effective adjunctively and in monotherapy; studies up to 8 weeks
Risperidone	Six studies; N=158; effective adjunctively and in monotherapy; studies < 12 weeks

MDMA in Anxiety Disorders

- Used adjunctively in treatment-resistant cases of PTSD
- Clinical dose of 125mg
- Pronounced effects lasts 3 to 6 hours

Obsessive-Compulsive Disorder



Epidemiology of Obsessive-Compulsive Disorder

- The lifetime prevalence of OCD in the general population is estimated at 2-3 percent.
- Some researchers have estimated that the disorder is found in as many as 10 percent of outpatients in psychiatric clinics.
- OCD is the fourth most common psychiatric disorder after phobias, substance-related disorders, and major depressive disorder.

Nonpsychiatric Clinical Specialists Likely to See Patients with Obsessive-Compulsive Disorder

- Dermatologist
- Family Practitioner
- Oncologist, infectious disease internist
- Neurosurgeon
- Obstetrician
- Pediatrician
- Pediatric cardiologist
- Dentist

Symptoms of OCD

Obsessions

- Contamination
- Pathological doubt
- Somatic
- Need for symmetry
- Aggressive
- Sexual
- Multiple obsessions
- Other

Compulsions

- Checking
- Counting
- Washing
- Need to ask or confess
- Symmetry and precision
- Hoarding
- Multiple comparisons

Treatment of OCD

○ SSRIs

- × Prozac
- × Luvox
- × Paxil
- × Zoloft

*Higher doses are often necessary.

○ Clomipramine (<250mg/day)

○ Augmentation Strategies

- × Behavioral Therapy
- × Valproate
- × Lithium
- × Carbamazepine
- × Venlafaxine
- × Pindolol
- × Phenezine
- × Buspirone
- × 5-hydroxytryptamine
- × L-tryptophan
- × Clonazepam

Case Discussion

- A 39 y.o. AA female was diagnosed with multiple sclerosis three months ago, and since then she has been having vertigo and neck spasms.
- She reports that she wakes up with a racing heart, chest heaviness, shortness of breath, faintness, and night sweats anticipating the vertigo and spasms.

Panic Disorder

- Usually begins in late adolescence to mid-thirties
- Higher probability if there is a first-degree relative
- Twin studies show a genetic component

“With or Without Agoraphobia”

- Agoraphobia is anxiety about being in places or situations where escape might be difficult (or embarrassing) or where help might not be available in the event of having a panic attack or panic-like symptoms.”
- Agoraphobia develops secondary to panic disorder in some patients

DSM-IV-TR Criteria for Panic Disorder

- At least 4 attacks occurred in a four-week period
- At least one attack has occurred totally “out of the blue”
- A fear of having another attack that has lasted > 1 month
- At least four sympathomimetic responses*

Sympathomimetic Responses for Panic Disorder

- Dyspnea
- Dizziness/faintness
- Palpitations
- Trembling or shaking
- Sweating
- Choking
- Nausea or abdominal distress
- Depersonalization or derealization
- Parathesias
- Hot/cold flashes
- Chest pain
- Fear of dying
- Fear of going crazy or doing something uncontrolled

Treatment for Panic Disorder

- Cognitive behavioral Therapy (effective in resolving 80% of cases)
- Pharmacotherapy
 - Paxil (FDA-approved)
 - Zoloft (FDA-approved)
 - Imipramine
 - Desipramine
 - Alprazolam (hi dose)
 - Diazepam
 - Clonazepam
 - Phelzine (may take up to 6 weeks to work)

Treatment for Panic Disorder

- Should start antidepressant and prn BZD at the same time
- Watch for stimulating effects from antidepressants
- Taper BZD after 1-2 weeks
- Current treatment options should not employ BZDs as sole therapy!

Case

- A 46 y.o. A.A. female has been dating the same guy for the last 6 years. He really likes her, but he tells you that he hates the fact that she “clams up” whenever family and friends come around.

Case Continued

- At work, she gave up an opportunity to become a manager, because she didn't want to "have to deal with people." She says she is content being assigned to manage the cosmetic section of department store instead of working in the clothing or shoe departments.

Case Continued

- Last summer, they were scheduled to take a five-day cruise, and she backed out of the trip a month before before claiming that she couldn't get off from work.

Case Continued

- During football season, he took her with him to hang out with his sister, and he got frustrated because she bought clothes to hang out at the club, but wouldn't go.
- When they got to the football stadium, but decided she didn't want to go inside the stadium (even though they had paid for tickets!).

Case Continued

- She didn't come to his graduation, but showed up at the celebration barbecue. While there, she stayed in the kitchen with the kids (all under age 7) and watched them watching a movie.

Case Continued

- On a recent trip to his mother's, the family had a community "fish fry," and she sat in the SUV for two hours until his sister forced her to come help the kids decorate Easter eggs.

Phobias

- Simple/Specific Phobias
- Social Phobias

Specific Phobias

- ☐ Acrophobia
- ☐ Agoraphobia
- ☐ Ailurophobia
- ☐ Hydrophobia
- ☐ Claustrophobia
- ☐ Cynophobia
- ☐ Myosophobia
- ☐ Pyrophobia
- ☐ Xenophobia
- ☐ Zoophobia
- ☐ Fear of heights
- ☐ Fear of open places
- ☐ Fear of cats
- ☐ Fear of water
- ☐ Fear of closed spaces
- ☐ Fear of dogs
- ☐ Fear of dirt and germs
- ☐ Fear of fire
- ☐ Fear of strangers
- ☐ Fear of animals

Treatment Options for Specific Phobias

- Behavior therapy
- Insight-oriented psychotherapy
- Hypnosis
- Family therapy
- Exposure therapy
- Pharmacotherapy

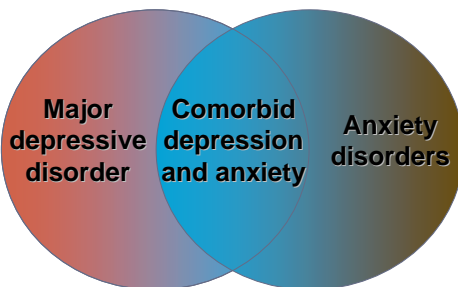
Social Phobia

- Defined as a persistent fear of one or more situations. The person fears they may act in a way or do something that will be humiliating or embarrassing in public. Avoidance behavior interferes with life.
- Examples: Using public bathrooms, speaking in public, signing name in public, eating in restaurants, or performance anxiety.

Treatment of Social Phobias

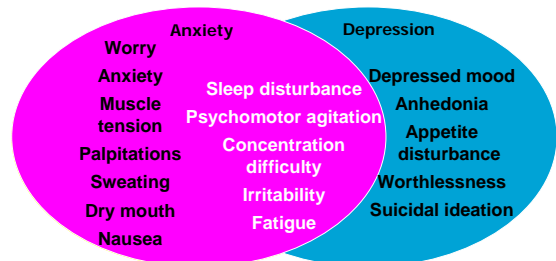
- Paxil*
- Beta-blockers:
 - Propranolol 10-40mg before performance
 - Atenolol 50-100mg for more generalized fears
 - Phenzelzine up to 90mg/day in divided doses.
 - Benzodiazepines: prn or regular dose

Continuum of Depression and Anxiety



Stahl SM. J Clin Psychiatry. 1993;54(1 suppl):33

Overlapping Symptoms of Depression and GAD



Choices of Antidepressant If:

Comorbid OCD Present

- Fluoxetine
- Paroxetine
- Sertraline
- Fluvoxamine
- Clomipramine

Comorbid Panic Disorder

- Fluoxetine
- Paroxetine
- Sertraline

Choices of Antidepressant If Co-morbid Anxiety Disorder Present

• Social Anxiety

- Paroxetine
- Sertraline
- Venlafaxine

• Generalized Anxiety

- Paroxetine
- Lexapro
- Venlafaxine

Closing Thoughts: Treatment Considerations for Anxiety Disorders

- Anxiety disorders usually coexist with depressive disorders.
- The antidepressants are preferred over the benzodiazepines.
- Antidepressants may take 8-12 weeks to work, and even longer in geriatric patients.
- There are limited treatment options for children.
- Novel Treatments have their limitations.

Concerns with Use of Atypicals

- Risk of Metabolic Syndrome
- Cost
- Polypharmacy
- Risk of heart attacks
- Concerns about suicide risk

Signs and Symptoms of Metabolic Syndrome

- Elevated waist circumference, greater than 35 inches for women and 40 inches for men. For people genetically at greater risk of diabetes, the circumference limit is slightly lower; 31 to 35 inches for women and 37 to 39 inches for men.
- Elevated level of triglycerides of 150 milligrams per deciliter (mg/dL) or higher, or if receiving treatment for high triglycerides.
- Reduced HDL (less than 40 mg/dL in men or less than 50 mg/dL in women) or if receiving treatment for low HDL.
- Elevated blood pressure of 130 millimeters of mercury (mm Hg) systolic (the top number) or higher or 85 (mm Hg) diastolic (the bottom number) or higher, or if receiving treatment for high blood pressure.
- Elevated fasting blood sugar (blood glucose) of 100 mg/dL or higher, or if receiving treatment for high blood sugar.

Monitoring Requirements for Metabolic Syndrome Prevention

- Journal of Psychiatric and Mental Health Nursing
Vol. 13 Issue 6 Page 730 December 2006

Poor Predictors of Response

- **Escitalopram**
 - Lower baseline symptom severity (Stein 2006)
- **Venlafaxine**
 - Hx of BZD use (Pollack 2003)
 - Co-morbid dysthymia (Perugi 2002)
 - Hx of depression or panic disorder (Pollack 2003)
- **Fluoxetine**
 - Duration of anxiety symptoms (Perugi 2002, Simon 2008)
 - Severity of psychosocial impairment (Rodriguez 2006)

QUESTIONS??

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