Phenomenology

Anxiety (definition): a "warning signal", functioning to make us aware of present or potential danger. The warning can be appropriate or inappropriate.

By definition, the anxiety disorders are primarily disorders of emotion. However, like other mental disorders, anxiety can affect all areas of the mental status exam (see table, right).

		Anxiety Disorders
General		Various physical manifestations: restless appearing, psychomotor agitation, shortness of breath, hyperventilation, stomach upset, chest pain, diaphoresis. May be ill kempt, or meticulously groomed (OCD). May display odd, ritualistic behaviors.
Emotiona	Mood	Anxious, fearful
	Affect	Frightened appearing, can be very intense.
	Process	can involve obsessive, persverative thougts.
	Thought	
	Content	Delusions, Hallucination.

Epidemiology

Anxiety disorders are the most prevalent of psychiatric disorders. Community samples have shown surprisingly high lifetime prevalences.

The ECA study demonstrated the following lifetime prevalences:

Anxiety Disorders: 15%
Generalized anxiety disorder: 8.5 %
Phobias 12.5%
Panic Disorder: 1.6 %
OCD: 2.5%

Additionally, One Month Prevalence Rates were determined as follows:

All Anxiety Disorders: *7.3%, distributed fairly equally across age groups, though somewhat lower in 65+*
Phobias: *6 %, distributed fairly equally across age groups, but women tended to have higher in young adulthood.*
Panic: *0.5 %, overall, distributed fairly equally across age groups, but women tended to have higher in young adulthood.*
OCD: *1.3 %, overall, tended to have higher in late adolescence and young adulthood.*

Furthermore, the National Comorbidity Survey demonstrated the following lifetime prevalences:

Any Anxiety Disorder: *25%*
Panic disorder: *3.5%*
Agoraphobia without panic: *5%*

Social Phobia: *13%*
Simple Phobia: *11%*
Generalized Anxiety Disorder: *5%*

Clinical samples have shown anxiety disorders to be a very common reason for presentation to primary care doctor, ER, etc. In terms of gender effects, anxiety disorders seem more common in women. They may decrease with age, and can also present differently at different ages. In children, an anxiety disorder can manifest as separation anxiety ("school phobia"). Elderly patients may tend more towards somatic presentations ("stomach problems", headaches, sleep problems).

Etiology/Pathology

Genetic influences are a factor. There is a high incidence of anxiety disorders passed to subsequent generations, as evident by family studies. In these studies, generally all the disorders are more common in first-degree relatives of affected individuals than the general public. Panic disorder has a 4-7X greater incidence in 1st degree relatives. Specific phobias may aggregate by type within families. Also, twin studies show strong genetic contribution to Panic Disorder. For example, in OCD concordance is higher for monozygotic than dizygotic twins.

The key neurotransmitters seem to be **catecholamines** ("fight or flight reaction") and serotonin modulation. Also, **the GABA receptor**, the primary inhibitory transmitter in the brain, plays an important role in the modulation of arousal and anxiety. Specific structures important in the etiology of anxiety disorders include the **Reticular Activation System (RAS)** and the so-called "**suffocation response.**"

Cortical Modulation plays an important role; key to this is the role of learning (classical and operant conditioning), as well as the role of stress, conflict, and neuroses (psychoanalytic theory).

Diagnostic tests have been used to further explore the pathogenesis of anxiety disorders. For example**, lactic acid, infusion**, and **carbon dioxide inhalation** bring out panic disorder. There is questionable evidence for suffocation response.

DSM-IV Diagnoses and Criteria for Panic Attacks:

Panic attacks must include **4 or more** of the following symptoms:

palpitations, pounding heart or increased heart rate
sweating
trembling or shaking
shortness of breath, smothering
choking sensation
chest pain
nausea
dizziness
derealization (feelings of unreality) or depersonalization
Feeling of losing control/going crazy
fear of dying
paresthesias
chills
A panic attack starts abruptly and peaks in about 10 minutes.

Diagnosis

SYNDROMES

Syndromes are defined not as disorders, but rather "building blocks for disorders" (like the "episodes" in mood disorders). These are not disorders, but building blocks for other disorders. The Syndromes include **panic attacks** and **agoraphobia**.

DSM-IV Criteria for Agoraphobia

Anxiety about being in a place or situation from which either
Escape is difficult or embarrassing, or
If a panic attack occurred, help might not be available
The situation:
Is avoided (restricting travel) or
Is endured, but with marked distress (a

THE DISORDERS

The Disorders are:
Panic Disorder with Agoraphobia
Panic Disorder without Agoraphobia
Agoraphobia without a History of Panic Disorder
Specific Phobia
Social Phobia
Obsessive-Compulsive Disorder
Posttraumatic Stress Disorder
Acute Stress Disorder
Generalized Anxiety Disorder
Anxiety Disorder due to a General Medical Condition, Substance-Induced Anxiety Disorder
and **Anxiety Disorder Not Otherwise Specified (NOS).**

DSM-IV Criteria for Panic Disorder (With or W/O Agoraphobia)

Recurrent unexpected panic attacks, and

At least 1 attack has been followed by 1 month+ of:
- concern about having additional attacks
- -Worry about the implications or consequences of the attack
- -Significant change in behavior relating to the attack

Specify presence or absence of agoraphobia

DSM-IV Criteria for Agoraphobia without Panic Disorder

The presence of **agoraphobia**

No history of **Panic Disorder**.

The disturbance is not caused by a general medical condition or by substances.

If an associated general medical condition, exists, the symptoms are

DSM-IV Criteria for Specific Phobia

Marked, persistent fear that is excessive or unreasonable, cued by a the presence or anticipation of a specific object or situation.

The phobic stimulus almost invariably provokes an immediate anxiety response.

The fear is recognized as excessive or unreasonable (not needed in children).

The phobic stimulus is avoided or endured with intense anxiety or distress.

Persons under age 18 must have the symptoms

Specific Types of Specific Phobias

Animal Type
Natural Environment type (heights, storms, water, etc.)
Blood-Injection-Injury Type

DSM-IV Criteria for Social Phobia.

Marked an persistent fear of one or more social or performance situations. The fear is of possible humiliation or embarassment.

The phobic stimulus almost always causes anxiety

The fear is recognized as excessive or unreasonable.

The feared situation is avoided or endured intense distress or anxiety.

The Global Criteria (see page ?).

DSM-IV Criteria for Posttraumatic Stress Disorder

The person experienced/witnessed/was confronted by an unusually traumatic event, which::
- Involved actual or threatened death/serious injury to the person or others, *and*
- Caused intense fear, horror or helplessness

The event is reexperienced through (1 or more of following):
- Intrusive, recurrent recollections
- Recurrent nightmares
- Flashbacks
- Intense distress in reaction to internal or external cues symbolizing/resembling the event.
- Physiological reactivity in response to these cues

Avoidance of the stimuli and numbing of general responsiveness shown by (3+):
- -Efforts to avoid thoughts, feelings or conversations about the trauma
- -Efforts to avoid activities, people or places associated with the event
- -Inability to recall important aspects of the event
- -Loss of interest/participation in significant activities
- -Feeling of detachment or estrangement from others
- -Restricted range of affect
- -Sense of foreshortened future

persistent symptoms of hyperarousal:
- -Insomnia
- -Irritability
- -Difficulty concentrationing
- -Hypervigilance
- -Exaggerated startle response

The above symptoms have lasted longer than one month.

DSM-IV Criteria for Obsessive Compulsive Disorder (OCD)

Either obsessions or compulsions:

Obsessions

Recurrent, perisistent thoughts or impulses, experiences (sometimes) as intrusive and inappropriate, and cause distress.

Thoughts aren't realistic worries about real problems

Person tries to ignore or suppress the obsessions.

The thoughts are recognized as such.

Compulsions.

Repetitive behaviors or mental acts that are done in response to an obsession.

The behaviors are meant to reduce distress, or prevent a feared event, but are not realistic.

DSM-IV Criteria for Generalized Anxiety Disorder

Excessive anxiety and worry occuring more days than not for at least 6 months, in regard to work, school or other activites.

It is difficult to control these worries.

The anxiety and worry are associated with 3+ of the following:

- restlessness, or feeling keyed up
- easy fatigue
- difficulty concentrating
- irritability
- muscle tension
- insomnia or restless, unrefreshing sleep

Aspects of another Axis I disorder do not provide the focus of the anxiety and worry.

OTHER ANXIETY DISORDERS:

Acute Stress Disorder is like PTSD, but less than 1 month.

Anxiety Disorder Due to a General Medical Condition, and Substance-Induced Anxiety Disorder can demonstrate as generalized anxiety, panic attacks, OCD symptoms, or phobic symptoms in the case of substances.

Anxiety Disorder NOS is a wastebasket diagnosis for anxiety symptoms not meeting the criteria for any specific disorder.

Differential Diagnosis

Important medical disorders that should be considered in the differential for anxiety disorders include **endocrine disorders** (pheochromocytoma, thyroid disorders, etc.), **cardiopulmonary disorders**, **and neurologic disorders**. **Substance induced disorders** mistaken for anxiety disorders *include withdrawal syndromes* (alcohol or tranquilizers), *and intoxication/therapeutic syndromes* (stimulants or others). Other psychiatric syndromes in the differential includemood disorders (anxiety can be misdiagnosed as, or comorbid with depression), psychotic disorders, sleep disorders, somatoform disorders, and eating disorders.

Comorbid Disorders

Commonly, mood disorders like depression can present comorbidly with anxiety, bringing to question genetic linkage or different forms of same disorder. Medical disorders with comorbidity include mitral valve prolapse and panic.

Course

Most tend to be chronic disorders. **Panic Disorder** tends to present late adolescence to early adulthood. It has perhaps a bimodal distribution (late adolescence and mid-30's). It can be chronic, but waxing and waning. At 6-10 years follow-up, 1/3 patients appear to be well, about 1/2 have improved but are still symptomatic, and 1/5-1/3 feel the same or worse. There is a high risk of relapse after (somatic) treatment. **Agoraphobia** may or may not improve if panic improves; it can become a "learned behavior."

Specific Phobia tends to begin in childhood. The situation type has a second peak in mid-20's (bimodal). It may spontaneously remit, but if it persists until adulthood, it becomes very chronic (perhaps 80% of those persisting to adulthood will be chronic). For **Social Phobia**, the onset is in the mid-teens. Patients may exhibit a premorbid history of shyness. Usually, social phobia is chronic, but it can fluctuate in severity. The onset of **OCD** is in adolescence or early adulthood. It presents earlier in males, who

may begin in childhood. The course is a chronic waxing and waning one. 15% have deterioration, and 5% have episodes with interepisode recovery. **PTSD** can present for the first time at any age. Half of patients with PTSD recover in 3 months; the rest may persist for long duration. The most important predictor is severity of trauma. Other factors include social support, family history, premorbid personality and psychological health may mitigate. Generalized Anxiety Disorder has an onset from childhood to early adulthood. It is, by definition, very chronic.

Treatment

SOMATIC TREATMENT FOR ANXIETY DISORDERS

Medications for anxiety include antidepressants and/or sedative hypnotics.

Antidepressants have gradually replaced sedative hypnotics for the first line treatment of many anxiety disorders. Several studies show antidepressants to be as effective as benzodiazepines for a variety of anxiety disorders (ex. Fluoxetine (Prozac) compared favorable against alprazolam (Xanax) for panic disorder). Their mechanism of action is presumed to be similar to that for their antidepressant effect, which is reasonable, as monoamines exert a modulatory influence on most other neurotransmitters in the brain, including GABA. However, antidepressants must be used preventively, on an every day basis. They are not effective in "as needed" dosing, and thus not appropriate for short term anxiety, or for quick relief of acute anxiety.

For more on antidepressants, see their description under Mood Disorders.

Sedative Hypnotics, benzodiazepines. There are three classes: 2-keto, 3-hydroxy and triazolo. 2-keto drugs include chlordiazepoxide, diazepam, prazepam, clorazepate, halazepam, clonazepam, and flurazepam. Many of these are prodrugs; they are oxidized in the liver (usually to active metabolites). They therefore tend to half long half-lives and are more susceptible to drug interactions and age effects. The 3-hydroxy drugs include oxazepam, lorazepam, and temezepam. These are conjugated in the liver (to inactive substances); thus, they have shorter half-lives, and are less affected by age and other drugs. The triazolo class includes alprazolam, triazolam and adinazolam. These are oxidized, but with more limited active metabolites. Thus, they are somewhat shorter acting than the 2-keto drugs. The mechanism of action relates to specific receptors on GABA receptors.

Indications for these medications include panic, generalized anxiety, specific and social phobias, mixed anxiety syndromes, insomnia, muscle tension, seizures, anesthesia, and

alcohol withdrawal.

Clinical Principles have dictated use in short term problems (< 2 weeks). However, the dilemma of long term treatment has arisen. One solution is a combination of psychotherapy and medication.

Side effects and risks include abuse potential, tolerance, withdrawal, dependence and addiction. There is also an overdose potential, with rare deaths as single agents. Other side effects are of the sedative variety-namely, sedation, dizziness, weakness, ataxia, decreased motoric performance, and falls in elderly. Finally, anterograde amnesia, nausea, hypotension (slight), and possibly dyscontrol have been shown in patients taking these drugs.

Of most concern are the side effects of tolerance and withdrawal, and the related (but not identical) fear of addiction in patients who take benzodiazepines regularly. Though perhaps overstated by some, a risk does exist. The best predictor of a likelihood of developing a problem like addiction with these drugs is a previous history of addition to other substances.

A related concern is the possibility of rebound anxiety once these drugs are stopped, which can be as serious as the original anxiety the drugs were meant to treat.

Because of the these worries, benzodiazepines are often reserved either for short term treatment of time-limited anxiety (ex. Worried preceding an upcoming surgery) or for intermittent anxiety (ex. If a person gets infrequent panic attacks, say, less than once a month). In both these cases, they may be preferable to antidepressants, in that antidepressants take weeks to work, and cannot be used intermittently (and it seems inappropriate to give daily antidepressants for an event that only happens once in a while).

Buspirone is a novel agent, in the class of drugs called azaspirones. Buspirone is believed to exert its antianxiety effect by blocking serotonin-1A (5-HT1A) presynaptic and postsynaptic receptors. There are no major effects on the GABA receptor. It is not useful for panic or other acute anxiety syndromes, but it may be useful for generalized anxiety. It works like an antidepressant; in other words, it requires regular dosing and takes several weeks to work. There is little abuse potential and few side effects. Buspirone lacks the benzodiazepines' sedative, muscle relaxant, or anticonvulsant actions and has no ability to affect benzodiazepine withdrawal symptoms. It is also surprisingly free of significant drug-drug interactions. However, it is not widely used; this either means that the drug isn't as effective in clinical situations than in "ideal" drug

marketing studies, or that the patients who are most likely to benefit may not be the complicated anxiety disorders seen by psychiatrists . Thus, there is a bias against the drug.

Other novel treatments include *beta blockers* for social phobias and *neurosurgery* for OCD.

PSYCHOSOCIAL/BEHAVIORAL TREATMENTS

Psychotherapies have been greatly successful for many of the anxiety disorders, sometimes more so than somatic treatments. An examples of well studied, effective treatments for anxiety is **cognitive behavior treatment** (CBT). CBT is based on learning theory, here the idea is that people learn to develop automatic responses of fear of dread in relation to a stimulus. What is learned can be unlearned, and much of CBT is spent teaching the patient to tolerate the triggers of anxietyy. In the case of phobias, the triggers are clear; in the case of panic disorder, the trigger is, in a sense the anxiety itself, and the patient learns to tolerate their anxiety. This treatment may be the only thing that helps agoraphobia if it is associated with the panic (which, otherwise, often persists long after medications have prevented the panic).

Other examples of psychotherapy for anxiety includes desensitization techniques for phobias. Often these are much more effective than any medication, and can truly cure the disorder, whereas medication will only provide symptomatic relief.

Other therapies may be more general, example group support is also offered for PTSD patients. However, again this can be very effective in a complicated disease that often doesn't respond well to medication along.

Some drugs commonly used for anxiety, sedation or for sleep

	type	approved for	equivalent dose (for benzos)	half-life	onset	metabolism
Diazepam (Valium)	Benzodiazepine	anxiety, alcohol withdrawal, muscle spasm, preop sedation, seizures	5 mg/day	long	very fast	oxidation
Chlordiazepoxide (Librium)		anxiety, alcohol withdrawal, preop sedation	10	long	fast	N-dealkylation
Oxazepam (Serax)		anxiety, alcohol withdrawal	15	short	slow	conjugation
Lorazepam (Ativan)		anxiety, preop sedation	1	short	fast	conjugation
Clonazepam (Klonopin)		seizures, panic disorder	0.25	long	fast	reduction
Alprazolam (Xanax)		anxiety disorders, panic disorder	0.5	medium	fast	oxidation
Flurazepam (Dalmane)		sleep	15	very long	fast	oxidation
Temezepam (Restoril)		sleep	15	medium	medium	conjugation
Triazolam (Halcion)		sleep	0.5	short	fast	oxidation
Zolpidem (Ambien)	omega-1 receptor agonists	sleep		2 hrs	½-1 hr	
Zaleplon (Sonata)		sleep		1 hr	½-1 hr	
Buspirone	azapirone (5-HT_{1A} agonist)	anxiety		N/A, usually given TID	½-1.5 hr	N/A
Diphrenhydramine (Benadryl)	Antihistamine	various: allergies, cold remedy.		3-10 hr	?	
Hydroxyzine (Vistaril, Atarax)		anxiety, pruritus, preop and postop sedation		?	2 hr	?
Antidepressants	*see the antidepressatn table*					