ANXIETY

Lois E. Brenneman, MSN, ANP, FNP, C

- Previously characterized as the "worried well."
- Prevalence in US is 13.3% of population or 19.1 million (National Institute of Mental Health)
- Predisposing factors: genetic, developmental, biochemical, experiential influences
- Genetic disposition implicated esp for panic disorders
- Negative health consequences esp increased risk psychopathology
- Therapy becoming more precise
  - Exact diagnosis re type anxiety is important
  - Example: panic disorder: use primary care services 3X as much as other patients
    - Cardiologists, neurologists, ER, GI specialists, repetitive work-ups
    - Problem likely to resolve with proper diagnosis and treatment
- Society and personal health costs are high
  - Anxiety disorders in US $65 billion (1994)
  - 31.8% of total cost mental disorders which includes indirect costs
    - $14.9 billion treatment
    - $49.6 for indirect costs (lost productivity)

- Anxiety encompasses a constellation of symptoms
- Characterized via irrational, involuntary thoughts and behavior
- Classifications
  - General anxiety disorder (GAD)
  - Obsessive-compulsive disorder (OCD)
  - Panic disorder
  - Phobias including social phobia
  - Post-traumatic stress disorder

- Defining element for all anxiety
  - Disruption of life by overt distress
  - Significantly reduced ability to carry out routine tasks
    - Personal; social
    - Vocational
  - Example: anxiety re exam-taking or public performance
    - Some nervousness is normal and beneficial
    - Decision to forfeit exam or cancel appearance signals impairment

Generalizing Anxiety Disorder (GAD)
- Formerly called overanxious disorder
- One of more chronic and recurrent of all psychiatric illnesses
- Affects 2.8% of US population or 4 million people
- Primary care practice: may be as high as 10-15%
- Unremitting excessive worry re: variety issues: family, health, work, etc.
- DSM-IV criteria
  - Must occur on majority of days for period of at least 6 months
  - At least 3 of the following must be present

Easy fatigability, difficulty concentration, irritability, muscle tension, restlessness, sleep disturbances
- Patients commonly present with physical complaints: lack insight re underlying root of anxiety
- Usual complaints:
  - Diaphoresis, headache, trembling
  - C/O feeling “tight all over my body”
- Frequently characterized as persistent “somatizers”
- Distinguishing from somatoform disorder can be challenging
- Cognitive or psychological manifestations may co-exist
  - Diminished ability to concentrate; impaired memory
  - Work, school performance may be compromised
  - Worry crowds out other thoughts: “Can’t shut off worry”
- Questions for interviewing patients to identify GAD
  - Do you tend to be worrywart by nature?
  - When you are tense at night, do you go over things in your mind to where thoughts can’t be shut off?
  - Do you feel tension between shoulder blades on wakening in the morning?
- Distinguishing GAD from appropriate anxiety
  - Insomnia in woman with sick child or impending divorce is appropriate
  - Woman with GAD will have insomnia with worry that her healthy children will fall ill
  - GAD are aware that fears are without a basis in reality but can’t control them
- Diagnosis often not taken seriously or regarded as residual diagnosis from excessive worry
- GAD is disabling and likely has root in pathophysiology
  - Can be disabling
  - Amygdala in brain is likely target (area which regulates fear, memory and emotion)

**Panic Disorder**
- Discrete, unprovoked episodes of intense fear
- Often patients feel as though they are having life-threatening medical event
  - Stroke, MI
  - Frequently report directly to ER
- Sensation of imminent and complete loss of control - report “I thought I was about to go crazy”
- Attacks are overwhelming: onset is precise
- Patients can usually cite time and place of first attack
  - Live in continual fear of next incident
- GAD, by contrast, has no particular onset - patients may report “I have always been nervous”
- Interview questions to help identify panic disorder
  - “Do you ever feel anxious suddenly and without understanding why?”
  - “Do you ever feel overwhelmed by feelings of panic?”
  - “Do you avoid places, people, or things because you feel uncomfortable without quite understanding why?”
- Ratio female: male is 2:1
- Prevalence rate is 1.7% or 2.4 million people per year
- Pattern of seeking care
  - 40% afflicted did not seek care
  - 39% of those seeking care visited internist or family physician
- Early diagnosis is key
  - Prevent prolonged functional impairment
  - Avoid unnecessary health costs
  - High risk suicide with panic attacks - monitor closely

- Diagnosing panic attacks
  - At least 4 symptoms in Table 1
  - One or more of criteria listed in Table 2

Table 1: COMMON SYMPTOMS OF PANIC ATTACK

| - Chest pain or discomfort                      |
| - Chills or hot flushes                         |
| - Derealization (feelings of unreality)        |
| - Depersonalization (being detached from oneself) |
| - Diaphoresis                                  |
| - Dizziness, unsteadiness, light-headedness    |
| - Fear of dying                                 |
| - Fear of losing control or going crazy        |
| - Nausea or abdominal stress                   |
| - Palpitations, pounding heart, tachycardia    |
| - Paresthesias                                 |

Table 2: QUANTIFYING CRITERIA FOR PANIC ATTACK

| - Persistent concern of at least 1 month’s duration about having another attack |
| - Worry about the implications or consequences of panic e.g. fear of loss of control or social humiliation |
| - Significant behavior change related to the attacks e.g. avoidance of situations in which panic attacks have occurred in the past |

- Presentation of panic attack
  - Burst of terror which seems to arise out of nowhere
  - No relevance to actual environment or what person is feeling at time of incident
  - Person typically freezes in steps, reaching out to hold something or balance
  - Sits or lies down
  - Sense of imminent doom pervades the experience
- Physiologic symptoms
  - Intense and bizarre
  - Often misdiagnosed in ER by physician as well as patient
  - Choking sensation; shortness-of-breath; or hyperventilation
  - Syncope is unlikely
  - Practiced controlled breathing can be helpful
  - Injury from fall is unlikely since anxiety raises BP (vs syncope where BP falls)
  - Lasts from 1-10 minutes but may be recalled as lasting for hours

- Neurologic component of panic attacks
  - Would seem to be precipitated from overactive control brain mechanisms
  - Brain misinterprets signals as more catastrophic than exist
  - Similar to false suffocation reflex from excessive CO2 exposure
  - May represent false-alarm mechanism triggering flight-or-flight response

Phobias

- Afflicts 8% or US population or 11.5 million people in any single year
- Three most prevalent forms: **agoraphobia, social phobia** and **specific (simple) phobias**
- Simple phobias: powerful - an admittedly irrational - fear of a specific entity or situation
  - Examples: snakes, heights, crossing bridges, flying, small spaces
  - Collective they are most common psychiatric illness in women in US
  - Second most common in US men older than 25
  - Affects women 2-3 times as likely as men
- Childhood phobias tend to resolve spontaneously (strangers, dark, large animals)
- Adult phobias resolve spontaneously without therapy only 20% of time
- Less than 20% of people with specific phobias seek help

- **Social phobia** - fear of being humiliated in front of other people
  - Results in afflicted persons avoiding ordinary events of professional/social interaction
    - Eating in restaurants, using public bathrooms or public telephones
  - Even small blunder may feel catastrophic error
  - Anything which focuses attention on patient is perceived as intolerable

- **Agoraphobia**: fear of places or situations where escape could be difficult or embarrassing
  - Compels persons to avoid all sorts of settings
  - Examples of common precipitating circumstances
    - Bridges, crowds, public transportation, stores, theaters, tunnels or any activity which requires waiting in line
  - Develops in 1/3 of the persons afflicted with panic disorders
  - Persons may avoid places where previously had panic attacks
  - Specific phobias may serve to trigger panic attacks
<table>
<thead>
<tr>
<th>Medical Conditions Suggested by Anxiety Symptoms</th>
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<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
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<tr>
<td>- Acute MI</td>
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<tr>
<td>- Angina pectoris</td>
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<tr>
<td>- Arrhythmias</td>
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<tr>
<td>- Congestive heart failure</td>
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<td>- Hypertension</td>
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<td>- Hypotension</td>
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<td>- Ischemic heart disease</td>
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<td>- Mitral valve prolapse</td>
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<td>- Pericarditis</td>
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<tr>
<td><strong>Endocrinologic and Metabolic</strong></td>
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<td>- Carcinoid syndrome</td>
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<td>- Cushing’s disease</td>
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<td>- Diabetes</td>
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<td>- Electrolyte imbalance</td>
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<td>- Hypercalcemia</td>
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<td>- Hyperkalemia</td>
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<td>- Hyperthyroidism</td>
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<td>- Hyponatremia</td>
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<td>- Parathyroid disease</td>
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<td>- Pheochromocytoma</td>
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<td>- Porphyria</td>
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<td><strong>Gastrointestinal</strong></td>
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<tr>
<td>- Irritable bowel syndrome</td>
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<td><strong>Gynecologic</strong></td>
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<td>- Menopause</td>
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<td>- Premenstrual dysphoric disorder</td>
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<td><strong>Hematologic disorders</strong></td>
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<td><strong>Immunologic disorders</strong></td>
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<td>- Anaphylactic shock</td>
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<td>- Anemia</td>
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<td>- Chronic immune diseases</td>
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<tr>
<td><strong>Neurologic</strong></td>
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<tr>
<td>- Brain tumor</td>
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<td>- Delirium</td>
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<tr>
<td>- Encephalopathy</td>
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<tr>
<td>- Epilepsy</td>
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<tr>
<td>- Essential tremor</td>
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<tr>
<td>- Familial tremor</td>
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<tr>
<td>- Parkinson’s disease</td>
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<tr>
<td>- Seizure disorder</td>
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<td>- Transient ischemic attack</td>
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<tr>
<td>- Vertigo</td>
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<tr>
<td><strong>Respiratory</strong></td>
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<tr>
<td>- Asthma</td>
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<tr>
<td>- Chronic obstructive pulmonary disease</td>
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<tr>
<td>- Dyspnea</td>
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<tr>
<td>- Emphysema</td>
</tr>
<tr>
<td>- Pulmonary edema</td>
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<tr>
<td>- Pulmonary embolus</td>
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SEDATIVES AND ANXIOLYTICS

PATHOPHYSIOLOGY ANXIETY

- Manifestations of a variety of physiologic processes
- Associated with uneasiness resembling fear
- Has some adaptive significance

- Increasingly become prevailing symptom in populations of industrialized societies
  - Also mental illness is increasingly pervasive
  - "Normal" anxiety usually related to specific events

- Pathologic anxiety occurs in response to specific stimuli
- Treatment
  - Modify stimulus (not always possible) or response to stimulus
  - Pharmacologic: sedative and anxiolytic drugs (diverse structure and actions)

- Originally treated by CNS depressants
  - ETOH
  - Barbiturates
    - Intro in 1950’s
    - Very sedating hence term sedative
    - Benzodiazepines (intro 1960’s)

ETHANOL (ETOH)

- CNS depressant with pharmacologic properties similar to other CNS depressants (barbiturates)
- Depressant but sometimes misperceived as stimulant
- Perceived stimulant caused by depression of certain cortical inhibitory control mechanism
- Alters reaction to pain
  - Increases pain threshold
  - Decreases concern for pain
- Alters response to other stimuli: light, sound and problem solving
- Potential for abuse: severe medical and socioeconomic problems
- Other alcohols (ethylene glycol and methanol) can cause serious medical problems.

PHARMACOKINETICS

- Rapidly absorbed from GI tract; absorption reduced by most foods
- Reaches high molar blood concentrations rapidly after ingestion
  - Rapid membrane absorption
  - High water solubility
  - Low molecular weight
- Blood levels drop rapidly due to tissue ethanol uptake
- Uptake especially rapid in highly vascular tissues e.g. brain
- High brain levels rapidly fall to redistribution - rapidly equilibrates with total body water
- Ethanol absorption and distribution is identical to water
- Ethanol a diuretic but renal excretion is not major route for termination of its effects.
  - Ethanol is excreted at same rate as is found in blood
  - Liver metabolism is major route of excretion
MICROSOMAL ETHANOL OXIDIZING SYSTEM

- Cytochrome P450 mixed-function oxidase system
- Increases its relative participation in ethanol oxidation at higher blood levels ETOH (levels >50 mg/dl)
- System is Induced by chronic ethanol consumption or drugs e.g. barbiturates

- Different affinities for ETOH account for relative difference in activities
  - Rate of ETOH metabolism is faster in the alcoholic than in the normal person
  - Difference is due to induction of ETOH dehydrogenase and cytochrome P450 systems
  - Induction of P450 system by ETOH will allow a cross-tolerance to other drugs.
  - Sober alcoholics are less sensitive to drugs that are detoxified by P450 system
- Acetaldehyde produced by these reactions is oxidized to acetate
  - Mitochondrial aldehyde dehydrogenase catalyzes reaction
  - Reaction requires NAD+ reduced to NADH

Acetaldehyde levels
- Alcoholics have higher levels of acetaldehyde with ETOH ingestion then non-alcoholics
- Difference is due to decreased number of functional mitochondria in alcoholic

Disulfiram (Antabuse): mechanism based on toxicity of acetaldehyde
- Inhibits aldehyde oxidase reactions by reacting with sulfhydryl groups on enzyme
- Significant illness results from even a small amount of ETOH with disulfiram
- Illness effects result from buildup of acetaldehyde
  - Throbbing headaches, nausea, vomiting, blurred vision, chest pains, difficulty in respiration, orthostatic hypotension and syncope.
- Signs and symptoms can progress to severe life-threatening illness
  - Respiratory depression, cardiovascular collapse, myocardial infarction, convulsions, sudden death.
- Other drugs have “Antabuse” effects
  - Griseofulvin, quinacrine, phenothiazines, phenylbutazone and sulfonylureas
METABOLIC CONSEQUENCES

- Ethanol is excellent caloric substitute for food
- ATP (energy production) can be form directly or indirectly from metabolism
  - Direct: acetate and NADH from aldehyde oxidase reaction (in mitochondria)
  - Indirect: NADH from alcohol dehydrogenase reaction via shuttle systems
- Oxidation of ethanal produces increased ratio of NADH to NAD+
  - Increased triglyceride synthesis
  - Hypoglycemia
  - Ketosis
  - Lactic acidemia
  - Hyperuricemia

LEGAL OR MEDICAL CONSIDERATIONS

- Ethanol is absorbed instantaneously and completely
- Metabolism does not rapidly effect blood concentration
- Ethanol distribution is equal in all water depots in body.
- Requires less than 2-3 drinks to become legally intoxicated
  - 100 mg/dl (0.10%) in most states
  - 80 mg/dl (0.08%) in MA and NC

<table>
<thead>
<tr>
<th>BLOOD LEVEL (mg/dl)</th>
<th>CLINICAL EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Increased sociability; individual may feel normal at this point.</td>
</tr>
<tr>
<td>30</td>
<td>Euphoria, decreased inhibitions, decreased muscular coordination</td>
</tr>
<tr>
<td>50</td>
<td>Gait disturbance, increased reaction time, lack of concentration</td>
</tr>
<tr>
<td>80 (0.08%)</td>
<td>&lt; 50% decrease in reflex reaction time, ataxia. Slurred speech, decreased mental and motor skills. Legal level of intoxication for MA and NC; 0.10% for most states</td>
</tr>
<tr>
<td>200</td>
<td>Difficulty in standing and walking; decreased sensations</td>
</tr>
<tr>
<td>400</td>
<td>Unconsciousness</td>
</tr>
<tr>
<td>400</td>
<td>Coma</td>
</tr>
<tr>
<td>500</td>
<td>Death (respiratory failure)</td>
</tr>
</tbody>
</table>

ETOH EQUIVALENTS

1 on whiskey (43% ETOH)
4 on wine (12% ETOH)
12 on beer (4% ETOH)
ACUTE EFFECTS OF ALCOHOL

<table>
<thead>
<tr>
<th>ETOH</th>
<th>CLINICAL EFFECTS</th>
</tr>
</thead>
</table>
| 50 mg/dl or less | - Increased sociability  
- Loss of inhibition  
- Decreased muscular coordination  
- Impaired judgement  
- Euphoria |
| Over 50 mg/dl | - Over 50 mg/dl  
- Gait disturbances  
- Increased reaction time  
- Lack of concentration |
| Over 100 mg/dl | - Ataxia  
- Slurred speech  
- Decreased short term memory  
- Decreased mental and motor skills |
| Over 200 mg/dl | - Over 200 mg/dl  
- Decreased perception of sensory stimuli  
- Difficulty walking and standing |
| Over 300 mg/dl | - Unconsciousness  
- Coma  
- Death by respiratory arrest  
- Death by cardiovascular depression |

NON-ETOH TOXIC ALCOHOLS

Methanol ("wood" alcohol)  
- Blindness, coma  
- Metabolizes to formic acid: severe acidosis

Ethylene glycol (antifreeze)  
- Severe acidosis - Renal damage

TREATMENT: administration of ethanol  
- Better substrate for alcohol dehydrogenase  
- Reduces oxidation of methanol or ethylene glycol

ETOH on MUSCLE

Relaxes smooth muscle  
Cardiac depression  
Vascular dilation  
Uterine relaxation.

CHRONIC EFFECTS OF ALCOHOL

Alcoholism

Tolerance develops from increased liver metabolism

CNS adaptation in chronic alcoholism  
- Pharmacodynamic tolerance  
- Cross tolerance

Alcoholic requires higher blood level of ETOH to become intoxicated (performance test)

Higher levels of inhalation anesthesia (not metabolized by liver) required

Acute ETOH intoxication inhibits metabolism of some drugs thus enhances effects (ETOH saturates P450 system)

Sensitivity certain drugs varies with sobriety  
- Less sensitive when sober  
- More sensitive when intoxicated due to inhibition of oxidation
CLINICAL EFFECTS OF ALCOHOLISM

Metabolic consequences of alcoholism in liver
- Hypoglycemia
- Fat accumulation thru NAD depletion (not available for critical pathways)
- Problems exacerbated by nutritional deficiencies
- Progressive fatty liver (becomes cirrhotic)
- Serious liver disease impairs all liver metabolism
- Cirrhosis: enhanced effects of drugs metabolized by liver
- Gynecomastia from accumulation of steroids

Gastrointestinal disturbances
- Inflammation and scarring
- Decrease absorption of nutrients and vitamins
- Worsen nutritional deficiencies
- ETOH strips protective lining of stomach
- More vulnerable to toxic action of NSAIDS (gastritis)

Central nervous system problems
- Sedation, decreased concentration, memory and mental powers
- Thiamine deficiency leads to Wernicke-Korsakoff syndrome
  - Asterixis, ataxia, confusion, weakness of EOM
  - Treatment: parenteral thiamine

Fetal alcohol syndrome
- Mental retardation, deficient growth
- Malformation of the face
- Other possible teratogenic effects
- Newborns consistently exposed to ETOH during preg

PHYSICAL DEPENDENCE - WITHDRAWAL AND TREATMENT

- Abstinence (withdrawal) signs/symptoms very severe - similar to barbiturate WD
- High mortality with alcohol withdrawal
- Signs/symptoms of withdrawal
  - Anxiety, insomnia, convulsions, muscle cramps
  - Trembling to include delirium tremens (DTs) and hallucinations
  - Nausea, vomiting, diarrhea, cardiovascular problems - all common
- Minor tranquilizers esp chlordiazepoxide (Librium) reduces all symptoms
- Paraldehyde is also effective but infrequently used
  - Excreted thru lungs
  - Strong odor
- Treatment of alcoholism complicated problems
  - Requires acceptance of problem
  - Psychological and peer support
- Disulfiram can be used but serious adverse effects
**BARBITURATES**

- Large class of **CNS depressants**
  - Di-substituted derivatives of barbituric acids (inactive)
    - Condensation product of malonic acid and urea
  - Barbiturate active only if there is an alkyl and/or aryl di-substitution at C-5 position

**PHARMACOKINETICS**

- Generally water insoluble in their nonionized forms
- Solubility in body dependent on pK of given compound
  - pK range of barbiturates (7/3-8.0) close to plasma pH (7.4)
  - Significant proportion of barbiturate is in the acid (nonionized) and base (ionized) form
  - Solubility (f) substituent at C-2 (chem structure)

- Solubility: The more soluble a barbiturate is the
  1. Faster the onset of action
  2. Shorter the duration of action
  3. Greater the hypnotic potency
  4. Greater the role of redistribution in terminating its effects

- Duration of action dictates clinical use
  - Short-acting thiopental: use as inducing agent
  - Long acting phenobarbital: anticonvulsant
  - Short to intermediate acting: hypnotics/sedatives
    - Secobarbital
    - Pentobarbital

**CESSATION OF EFFECTS - REDISTRIBUTION**

Wide variability among various barbiturates

**Phenobarbital**: effects terminated by normal urinary excretion
**Secobarbital** and **pentobarbital**: terminated by normal liver function

**Thiopental**

Not effected by normal liver or kidney function but are controlled primarily via other phenomenon, redistribution.

Redistribution

- Initial rapid spike in blood concentration after IV injection
- Followed by rapid falling off primarily due to transfer to heavily vascularized tissue (eg brain)
- Brain levels drop off when blood levels decrease sufficiently
- Muscles and viscera pick up and let go but at slower rate (less vascular)
Adipose Tissue and Thiopental
- Picks up thiopental slowly (poor vascular)
- Does not readily let go (not very lipid soluble)
- Thiopental accumulates in adipose tissue
- Thiopental only used as pre-anesthesia agent
  - Rapid onset; short duration of action
  - Adipose tissue accumulates to point of saturation w repeated dosing.
  - Once brain adipose tissue is saturated, more drug is dangerous (builds up in blood and brain)

- Redistribution: Problems occur where drug actions are terminated primarily by redistribution
  - Role of metabolism and excretion very important multiple injections
  - Tissue that accumulates drug is constantly releasing small amounts into circulation
  - Released drug is metabolized and excreted
  - Tissue accumulation and saturation hastened where metabolism and excretion are impaired.
  - Rate of thiopental metabolism in human liver is 10%/hr

MECHANISM OF ACTION
- Depress all excitable tissues but esp CNS
- Decrease excitatory post-synaptic potentials
- Inhibit certain multisynaptic reflex systems
- Inhibition of reticular activating system is probable reason for hypnotic effect.
- Depressant effect:
  - Ability to stimulate a chloride channel directly
  - Leads to chloride influx and hyperpolarization.

BIOLOGICAL EFFECTS
- Depress CNS in a dose-dependent and reversible fashion from sedation to coma
- Sedation: relieves anxiety, removes inhibition
- Hypnosis: induction and increase of sleep duration
- Barbiturate induced sleep
  - Appears normal in most respects
  - Reduction in REM sleep associated w dreaming
  - Rebound increase in REM sleep - associated with nightmares and restlessness
- Anesthesia
  - Amnesia
  - Reflex suppression
  - Loss of consciousness
- Respiration is depressed
  - First via depression of respiratory center
  - Higher doses: chemoreceptor depression
  - CO2, H+ and oxygen receptors
  - Hypotension and cardiovascular collapse may ensue
- Tolerance develops due to
  - Increased metabolism: drug disposition tolerance
  - CNS "adaptation": pharmacodynamic tolerance
TREATMENT OF BARBITURATE OVERDOSE

Symptomatic

- Maintenance of respiration
- Gastric lavage
- Hemodialysis
- Urine alkalization (only for phenobarbital)
  - Promote urinary excretion
  - Phenobarbital effects are terminated by renal excretion

ADVERSE EFFECTS:

- **CNS depression** is most important problem (esp since additive with other drugs)
  - ETOH, benzodiazepines, H1 receptor antagonists
  - Tricyclic antidepressant, phenothiazines

- **Microsomal enzyme induction**:
  - Occurs with barbiturates
  - Leads to faster metabolism of drugs and hormones
  - Normally metabolized by hepatic P450 system

- **Acute intermittent porphyria**
  - May be precipitated by barbiturates
  - Barbiturates must be absolutely avoided in this condition

- **Associated with severe dermatitis**
  - Exfoliative dermatitis
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis (rare but catastrophic)
  - Avoid concurrent administration of penicillin and sulfonamides
    - Increases likelihood of occurrence of dermatitis
    - Antibiotics associated with same risks
  - Prompt cessation and treat with antihistamines

- **Overdosing**
  - Accidental overdosing by addict or suicide attempt
  - Addict may become tolerant of desired (hypnotic) effect faster than the toxic effects
    - Experiences decreasing therapeutic index
  - LD50/ED50 decreasing: ED50 decr faster LD50
  - Addict may OD as attempts dose high enough for desired effect
    * LD = lethal dose  ED = effective dose

- **Psychological dependence**: leads to chronic use to reduce anxiety
- **Physical dependence**: leads to withdrawal symptoms similar to ETOH
<table>
<thead>
<tr>
<th>DURATION of ACTION</th>
<th>NAME</th>
<th>CLINICAL USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-short</td>
<td>Thiopental</td>
<td>Preanaesthetic</td>
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<tr>
<td></td>
<td>(Pentobarbital)</td>
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<tr>
<td>Short-intermediate</td>
<td>Amobarbital</td>
<td>Anesthetic</td>
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<td></td>
<td>(Amytal)</td>
<td>Hypnotic</td>
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<td></td>
<td>Hexobarbital</td>
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<td>(Evipan)</td>
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<td>Pentobarbital</td>
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<td>(Nembutal)</td>
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<td>Secobarbital</td>
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<td>(Seconal)</td>
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<td>Phenobarbital</td>
<td>Sedative</td>
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<td>(Luminal)</td>
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BENZODIAZEPINES

- Emerged as most important sub-group of sedative-hypnotics
- Widespread use in "age of anxiety"

MECHANISM OF ACTION

- Bind to specific receptors
- CNS receptors: high affinity - *thalamus, limbic system* and *cerebral cortex*
- PNS receptors with low affinity
- Bind receptors: induce a conformational change
- Increase in availability of GABA receptors for GABA
- Higher chloride influx and hyperpolarization

Barbiturates promote higher chloride influx directly
Benzodiazepines do so indirectly via GABA

PHARMACOKINETICS:

- Most are lipid soluble - except oxazepam (Serax)
- Lipid solubility: *easy penetration thru blood-brain barrier*
- All except clorazepate (Tranxene) well absorbed GI tract
- Metabolized by hepatic enzymes - metabolic pathways vary considerably
  - Diazepam (Valium) half life: 50-150 h
  - Temazepam (Restoril) half life: 5-8 hrs

METABOLISM

- First dealkylated then conjugated mostly to glucuronic acid
- Many of the dealkylated metabolites are active with long plasma half-lives
  - Chlordiazepoxide (Librium) converted to desmethyldiazepamoxide: *both active*
  - Diazepam (Valium) converted to desmethyldiazepam: *both active*

- Excessive sedation occurs with long acting drugs
  Continuous therapy for several days with long-acting drugs (diazepam, chlordiazepoxide) may lead to accumulation of active metabolites

BIOLOGIC EFFECTS:

- Many effects similar to barbiturates:
  - Sedation (low doses), hypnosis (higher doses) and some anesthesia
  - Rarely cause medullary depression and coma
- Potentiate other CNS depressants
- Respiratory depression from high doses (esp children and elderly)
- No autonomic nervous system effects
- No antipsychotic activity
- No extrapyramidal adverse effects
- Have anticonvulsant effects (like barbiturates; unlike phenothiazines)
- Certain agents have central muscle-relaxing action (unique property)
  - Diazepam (Valium)
- Tolerance and dependence may develop
- Do not block conditioned responses at low doses
## PHARMACOKINETICS OF BENZODIAZEPINES

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ELIMINATION HALF-LIFE (hr)</th>
<th>METABOLITES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam (Versed)</td>
<td>1-2</td>
<td>Inactive</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>3-5</td>
<td>Active: a-hydroxy triazolam</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>4-10</td>
<td>Inactive: glucuronides</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>5-8</td>
<td>possibly active</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>5-30</td>
<td>Active: desmethyl derivative, demoxepam, oxazepam</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>10-18</td>
<td>Inactive: glucuronides</td>
</tr>
<tr>
<td>Alprazolam (Xanax)</td>
<td>12-15</td>
<td>Active: a-hydroxy alprazolam</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>12-24</td>
<td>Active: desmethyflunitrazepam</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>18-50</td>
<td>Inactive: nitro reduction</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>24-36</td>
<td>Inactive: nitro reduction</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>24-100</td>
<td>Active: desalkyl derivative, others</td>
</tr>
<tr>
<td>Prazepam (Centrax)</td>
<td>30-120</td>
<td>Active: desmethyldiazepam</td>
</tr>
<tr>
<td>Clorazepate (Tranxene)</td>
<td>50-100</td>
<td>Active: desmethyldiazepam, oxazepam</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>50-150</td>
<td>Active: desmethyldiazepam, temazepam, oxazepam</td>
</tr>
</tbody>
</table>
BENZODIAZEPINES
with indication for ANXIETY

Alprazolam (Xanax)
Diazepam (Valium)
Chlordiazepoxide (Librium)
Lorazepam (Ativan)
Midazolam (Versed)
Oxazepam (Serax)

BENZODIAZEPINES AS HYPNOTICS

Flurazepam (Dalmane): not useful as anxiolytic
Oxazepam (Serax), Temazepam (Restoril) commonly used
Generally overused for insomnia without underlying anxiety
Other drugs equally effective with less potential for abuse
  - H1 receptor antagonists: Benadryl, Atarax
  - Zolpidem tartrate (Ambien)
  - Phenothiazines: Promethazine (Phenergan)
Other hypnotics also with abuse potential
  - Barbiturates
  - Benzodiazepines
  - Chloral hydrate

Status epilepticus and muscle spasticity - diazepam (Valium)

Delirium tremens - chlordiazepoxide (Librium)
Absence seizures - clonazepam (Klonopin) commonly used
Anxiety states with/without depression
Acute hallucinogen-induced (LSD) toxic psychosis

Panic attacks
  - Alprazolam (Xanax) approved
  - Clonazepam (Klonopin) approved
  - Low dose SSRI are also effective

Social phobias: benzodiazepines, SSRI, MAO
Performance anxiety - "stage fright"
  - Propranolol (Inderal) is also effective
Night-time sedation and sleep (Hypnotic)

CLINICAL USES

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ADVERSE EFFECTS:

- High therapeutic index
- Adverse effects are minor
- Major problem with chronic use: dependence

- **Abstinence syndrome**: resembles ETOH and barbiturates withdrawal
  - Tremors - can be severe
  - Convulsions
  - Muscle cramps, abdominal cramps
  - Sweating

- Potentiation of CNS depressants eg ETOH
- **Paradoxical rage** may be induced - thought to be due to central disinhibition
- Problems with accumulation of drugs due to long half lives
  - Approximately 24 hours
  - Even longer half-lives for active metabolites
  - Latency period before withdrawal appears due to long half-life

**Flumazenil (Romazicon)**: major advance in treatment of acute toxicity
- Receptor antagonist (analogous to naloxone-Narcan for opioids)
- 0.1-1.0 mg IV over 10 min
- Caution to avoid ppt acute WD eg seizures
- Repeat antidote (t1/2 = 60-90 min)
  - Where toxicity is due to long-acting benzodiazepines
  - To avoid decompensation and respiratory arrest

OTHER ANXIOLYTICS

**Hydroxyzine (Atarax, Atarax Syrup, Vistaril, Vistaril Suspension)**
- Antihistamine with indications as antihistamine and anxiolytic
- Indication: anxiety associated with psychoneurosis or organic disease
- Potentiates CNS depression with alcohol and other CNS depressants
- Contraindicated: early pregnancy
- Precaution: therapy > 4 months
- Adverse reactions: drowsiness, dry mouth, tremor, convulsions

**Prochlorperazine (Compazine, Compazine Spansules, Compazine Syrup)**
- Phenothiazine; also used as an antiemetic
  - Indication: short-term treatment of nonpsychotic anxiety
  - Adverse reactions:
    - Drowsiness, may mask emetic signs of disease, hypotension, lowered seizure threshold, extrapyramidal symptoms, others

**Phenothiazine (Stelazine)**
- Phenothiazine
  - Indication: short-term treatment of non-psychotic anxiety
  - Adverse reactions: tardive dyskinesia, drowsiness, blood dyscrasia, hypotension, others
  - Potentiates CNS depression with other agents
Buspirone (BuSpar): prototype of class aryl-piperazine

- Contain an azaspirodecaneonedione structure which may not be critical for anxiolytic activity
- Potent antianxiety but distinct from benzodiazepines
- Acts as a selective 5-HT 1A receptor agonist
- Leads to inhibition (possibly indirectly)
- Indication: Anxiety
- Promoted for generally anxiety disorder
- Requires weeks to produce therapeutic effect
- Does not influence GABA receptors
- No anticonvulsant or sedative properties
- Little risk of tolerance or dependence
- Faster on set of benzodiazepines is due to rapid effect on sleep
- Do not use in patients with severe insomnia as symptom of anxiety
- No cross tolerance
- Does not protect against symptoms of benzodiazepine withdrawal
- Adverse effects: nausea, dizziness, headache, restlessness (indicate need to reduce dose in half for 1-2 weeks)

Venlafaxine (Effexor) (see antidepressants for profile)
Indicated for general anxiety disorder

Selective Serotonin Reuptake Inhibitors (SSRI)

- Originally indicated for depression
- Two class members indicated for panic disorder
  Sertraline (Zoloft)
  Paroxetine (Paxil)
- Growing body of evidence supporting use of other SSRIs, as well
- One class member - Paroxetine (Paxil) - is indicated for social anxiety

- May be of benefit in treatment of generalized anxiety disorder esp with panic attacks
- Documented benefit for posttraumatic stress disorder
- Bulimia nervosa: fluoxetine (Prozac)
- Certain class members have FDA indication of obsessive-compulsive disorders
  Fluvoxamine maleate (Luvox)
  Paroxetine (Paxil)
  Fluoxetine (Prozac)
  Sertraline (Zoloft)

Some evidence suggests that obsessions respond preferentially to SSRIs, whereas compulsions are best addressed via behavioral interventions with medications

65%-75% of patients respond to first trial of therapy with 90% responding to sequential trials - alleviate symptoms but do not cure illness
PANIC DISORDER

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks - Discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes

1. Palpitations, pounding heart
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Felling dizzy, unsteady, lightheaded or faint
9. Derealization (feeling of unreality) or depersonalization
10. Feeling of losing control
11. Fear of dying
12. Parathesias (numbness or tingling)
13. Chills or hot flushes

Agarophobia occurs in 95% of patients with panic disorders

Persons avoid phobic situations to point of being unable to leave their homes (untreated sometimes for an entire life)

SOCIAL PHOBIA

Persistent and disproportionate fear in a performance or social setting

Hypersensitivity to criticism

Low self esteem, at times including the indirect criticism of others as in test-taking

May be generalized to multiple situations or specific to particular event

Life-long problem handled by avoidance

POST TRAUMATIC STRESS DISORDER

Traumatic experience or exposure to a traumatic event that is re-experienced persistently

Resulting in avoidance of stimuli associated with the event and persistent symptoms of increased arousal
HYPNOTICS

Benzodiazepines (see Anxiolytics)

Barbiturates (see Anxiolytics)

Hydroxyzine

- H1-receptor antagonist with sedative and anxiolytic properties
- Sedation is prominent at doses required for anxiolytic effect
  - Sedation decreases with continuous use
  - Anxiolytic effect remains

Chloral hydrate

- Absorbed from GI tract but irritating if not properly diluted or taken on empty stomach
- Rapidly metabolized to trichloroethanol
  - Also has hypnotic properties
  - Both distribute throughout body
  - Conjugated to glucuronide and excreted in urine
- Does not have analgesic activity
- Narrow therapeutic index prevents use as anesthetic agent
- Increases sleep duration and decreases awakenings
  - Does not effect REM sleep
  - No rebound REM on d/c

ADVERSE EFFECTS

- Unpleasant taste, nausea, flatulence and epigastric pain
- Ataxia, light-headedness, malaise also occur.
- Toxic doses:
  - Cause cardiac suppression via reduced contractility
  - Can lead to severe respiratory depression
  - Severe hypotension
- Tolerance, physical dependence and addiction occur
- Sudden withdrawal may lead to seizures and death
- Both intoxication and withdrawal are managed with barbiturates

BENZODIAZEPINES

Hypnotic Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triazolam (Halcion)</td>
<td>2 h</td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>8 h</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>9 h</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>12 h</td>
</tr>
<tr>
<td>Alprazolam (Xanax)</td>
<td>15 h</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>24 h</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>&gt; 50 h</td>
</tr>
</tbody>
</table>

ALSO HYPNOTIC INDICATIONS

Quazepam (Doral)
Estazolam (Prosom)

Bold indicates FDA indication

BARBITURATES

Hypnotic Indications

Butabarbital (Butisol Na)
Pentobarbital (Nembutal)
Mephabarbital (Mebaral)
Zolpidem (Ambien)

Class: imidazopyridine
Pregnancy category B; Controlled substance class: Schedule C-IV
Nonbenzodiazepine hypnotic with clinical similarities and less undesirable side-effects

INDICATION
- Short-term insomnia (7-10 days)
- Often prescribed for long-term use
- Reevaluation if needed more than 2-3 wks
- Do not prescribe quantities exceeding 2-3 weeks supply

CLINICAL CONSIDERATIONS
Avoids some unwanted effects of benzodiazepines
Maintains architecture of sleep
- Preservation of stages of sleep
- No classic increased wakefulness during last third of night
- Can decrease sleep latency; increase duration of sleep
- Preserves deep sleep (stages 3 and 4) in hypnotic doses
Effective for short-term and chronic insomnia
No evidence of residual next-day effects
No respiratory depression
No evidence of next-day residual effects

No withdrawal syndrome; no dependency
No rebound insomnia
Abuse potential at therapeutic doses is low
40 mg similar (not identical) to diazepam 20
10 mg virtually identical to placebo
Expected anterograde amnesia occurs at 10 mg

DOSING
Usual dosage: 10 mg/d
5 mg for elderly or debilitated
Downward adjustment recommended when used with other CNS-depressants
Dosing should not exceed 10 mg

MECHANISM
Non-benzodiazepines acting on benzodiazepine receptor complex
Preferentially binds the Omega1 receptor
Benzodiazepines non-selectively bind all three
(Omega 1, Omega 2, Omega 3)
Selective binding lost at higher dosing
May explain differing profile vs benzodiazepines
- No myorelaxant
- No anticonvulsant effects

AMNESIA AND HYPNOTICS
Hypnotics commonly cause anterograde amnesia
Amnesia not usually problematic since most hypnotics taken before sleep
"Traveler's amnesia" occur when hypnotics are taken during travel and person wakes before effect of medication is gone
Amnesia is not common with zolpidem
Hypnotics should only be taken when able to devote 7-8 hours to

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PHARMACOKINETICS

Rapid acting, short half-life (2.5 hrs)
Rapid absorption from GI tract;
Converted to inactive metabolites eliminated primarily by renal excretion
 Linear kinetics; no accumulation at therapeutic dosing
Hepatic metabolism: modify dosing with hepatic insufficiency
No adjustment for renal insufficiency

CONTRAINDICATIONS: none

INTERACTIONS

Additive effects with other CNS depressants
Additive effect with alcohol
Effects reversed with flumazenil
Adverse effects are overall low and infrequently occurring
Dizziness, daytime drowsiness, diarrhea, drugged feeling, amnesia

Zaleplon (Sonata)

Class: pyrazolopyrimidine;
Pregnancy category C; Controlled substance class: Schedule C-IV
Nonbenzodiazepine hypnotic with elimination half-life of approximately 1 hour

INDICATION: Short-term treatment of insomnia
- Limit RX to 7-10 days; reevaluate if taken more than 2-3 wks
- Do not RX over 1 mo supply

CLINICAL CONSIDERATIONS
- Decreases sleep onset time; no increase in total sleep
- Short half-life permits use during mid-sleep awakenings
- Can take anytime at least 2-3 hrs prior to awakening time
- Lessens concerns for daytime consequences
- Expected hypnotic memory impairment occurs at 1 hour
  - No longer present as early as 2 hours; none after 3-4 hrs
  - Next day amnesia: zaleplon (3%) vs placebo (1%)
  - Effect is dose dependent
- No next day somnolence (same as placebo); no next-day anxiety
- No rebound insomnia at therapeutic dosing
- No withdrawal emergent phenomena
- No respiratory depression at therapeutic doses
- Tolerance: none at therapeutic doses
- Abuse potential
  - Similar to benzodiazepines at high doses (25, 50, 75)
  - Unknown at therapeutic doses

DOSING: 10 mg HS
- Reduce to 5 mg with mild-moderate hepatic impairment
- No adjustment need for mild-moderate renal impairment
MECHANISM

- Interacts with GABA-BZ receptor complex
- Binds selectively with the omega-1 receptor
- GABA-BZ also produces pharmacology some properties of benzodiazepines *

* Sedative, anxiolytic, muscle relaxant, anticonvulsant

PHARMACOKINETICS

- Rapid acting (peak concentrations 1 hour) with short half life (1 hour)
- No accumulation with qd dosing; pharmacokinetics are dose proportional
- Hepatically metabolized; all metabolites are inactive
- Renally excreted as metabolites (less than 1% excreted unchanged in urine)

CONTRAINDICATIONS: none

INTERACTIONS

- Drugs which are potent inducer of CYP3A4 could lead to ineffectiveness
  - CYP34A in normally only minor metabolizing enzyme of zaleplon
  - Potent inducer (CYP3A4) could lead to ineffectiveness
    - Rifampin, phenytoin, carbamazepine, phenobarbital
  - Zaleplon is potentiated by drugs which inhibit aldehyde oxidase:
    Reduce dose to 5 mg with cimetidine coadministration

WARNINGS

Short half-life considerations limit ingestion to
- Immediately prior to going bed
- After going to bed when patient experiences difficulty in falling asleep
Avoid use with hazardous occupations requiring mental alertness
Situations requiring motor coordination (operating machinery, driving motor vehicle)
Additive and potentiating effects with other CNS-depressant agents
  Psychotropic agents, anticonvulsants, antihistamines, ethanol, drugs producing CNS depression

ADVERSE EVENTS

Overall low
Drowsiness, amnesia, paresthesia, abnormal vision, hyperacusis, parosmia, anorexia, depersonalization

Melatonin

- Indole-amine secreted by the pineal gland at night; function in humans is elusive
- Altered environmental lighting influences pineal gland secretion
- Implicated in sleep/wake cycle
  Useless in treating jet lag and shift work sleep disturbance
  Melatonin taken HS in new time zone attenuates jet lag
- Promoted in lay press as hypnotic agent
  - Use in nonmelatonin-deficient insomnias is controversial
  - Beneficial for no more than 5%-10% of insomniacs
Sedating Antidepressants in Small Doses

- Nortriptyline (Pamelor) 25 mg to 50 mg HS
- Trazodone (Desyrel) 25 - 100 mg HS

Safety and efficacy of this practice yet to be fully established
Commonly used with fibromyalgia to treat the associated sleep deficits

Sleep Hygiene Approaches to Insomnia

- Patients benefit from counseling for sleep and insomnia
- **Daytime napping to be avoided** - creates "vicious cycle" phenomenon
- Light bedtime snack esp carbohydrates or protein may sustain sleep
- Avoid caffeine especially in late afternoon or evening
- **Limit alcohol** intake esp in evening
  - Promotes poor quality sleep
  - Frequent awakenings
- Regular exercise program morning or afternoon may promote sleep

<table>
<thead>
<tr>
<th>SLEEP HYGIENE INSTRUCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Rules&quot; Patients must Follow</td>
</tr>
</tbody>
</table>

1. Lie down intending to go to sleep only when you feel sleepy.
2. Use your bed only for sleep.
3. If you are unable to fall asleep, get up and go into another room. Stay up as long as you wish and then return to the bedroom to sleep. Although we do not want you to watch the clock, we want you to get out of bed if you do not fall asleep immediately. The goal is to associate your bed with falling asleep quickly! If you are in bed more than about 10 minutes without falling asleep and have not gotten up, you are not following this instruction.
4. If you still cannot fall asleep, repeat rule 3. Do this as often as is necessary throughout the night.
5. Set your alarm and get up at the same time every morning irrespective of how much sleep you had during the night. This rule includes weekends and days off work.
6. Do not nap during the day.

Adapted from Rakel: Conn’s Current Therapy 2000, 52nd ed., Copyright 2000 W. B.