ANXIOLYTICS AND SEDATIVE HYPNOTICS

I. ANXIETY

A. DEFINITION
   1. May be adaptive to threat or danger
   2. “Fight or Flight” reaction for survival
   3. Must be maladaptive to be a psychiatric disorder

B. GENERALIZED ANXIETY DISORDER (GAD)

DSM IV CRITERIA:

SYMPTOMS:

1. Excessive anxiety and worry (apprehensive expectation) > 6 months
2. Difficulty controlling the worry
3. Anxiety and worry with three of six symptoms > 6 months
   (only one for children)
   a) restless or keyed up or on edge
   b) easily fatigued
   c) difficulty concentrating or mind going blank
   d) irritability
   e) muscle tension
   f) sleep disturbance

C. Focus of anxiety and worry is not a feature of Axis I Disorder

D. Must impair social, occupational, or other areas of function
E. Not related to physiological effects of substances

F. PREVALENCE

   a) 10% of population in USA
   b) many are excluded due to 6 month criteria
   c) personality scales high on neuroticism
   d) develops in decade between late teens and early 20's
   e) chronic and episodic
   f) more common in:
      -women > men
      -unmarried > married
      -racial-ethnic minority > majority
      -low socioeconomic > middle or high SES
   g) highest current prevalence is among middle-aged people due to high lifetime risk (cohort effect)

II. NEUROBIOLOGY OF GAD

A. GENETICS

   1. Genes may influence expression of key neurotransmitters
   2. Familial syndrome
   3. High rate of co-morbidity with other disorders
   4. Genetic predisposition can be modified by environmental demands

B. EPIDEMIOLOGY

   1. Estimated at 15%
   2. 12% are simple phobias
3. 1-2% are panic disorders
4. 2% are OCD
5. 2-5% are GAD
6. 17% PTSD (20% war veterans)

III. DSM IV CLASSIFICATIONS OF ANXIETY DISORDERS

A. PANIC DISORDER WITHOUT AGORAPHOBIA
B. PANIC DISORDER WITH AGORAPHOBIA
C. AGORAPHOBIA WITHOUT HISTORY OF PANIC DISORDERS
D. SPECIFIC PHOBIA
E. SOCIAL PHOBIA
F. OBSESSIVE-COMPULSIVE DISORDER
G. POSTTRAUMATIC STRESS DISORDER
H. ACUTE STRESS DISORDER
I. GENERALIZED ANXIETY DISORDER (INCLUDES OVERANXIOUS DISORDER OF CHILDHOOD)
J. ANXIETY DISORDER DUE TO
   a) medical condition
K. SUBSTANCE-INDUCED ANXIETY DISORDER
IV. NEUROCHEMISTRY OF ANXIETY

A. GABA

1) Widely distributed in brain and CNS
2) Main inhibitory NT
3) Benzodiazepine and GABAₐ receptors are part of same macromolecular complex
   a. different binding sites
   b. functionally coupled
   c. regulated allosterically
4) GABAₐ receptor dysfunction in anxiety disorders
5) Benzodiazepine receptors are located in frontal cortex, hippocampus and hypothalamus (areas associated with neural circuitry of fear and anxiety)
6) GAD – patients found to have low levels of peripheral lymphocyte benzodiazapine receptors (PBR)
7) PBR's normalize after treatment with benzodiazepines
8) GAD may reflect
   a. abnormal decrease of PBRs
   b. found in obsessive compulsive disorder
   c. not in Panic Disorder
   d. rate of synthesis increases with recovery
   e. PBRs may modulate central GABAₐ receptor function
   f. May also involve dysregulation of benzodiazepine and GABA Coupling System
B. NORADRENERGIC SYSTEM

1. Active with acute and chronic stress
2. NE activity is increased in GAD
3. May reduce alpha-2 receptors
4. Inhibition of alpha-2 receptors presynaptically results in increased anxiety

C. SEROTONERGIC SYSTEM

1. 5HT in cortical and limbic areas is increased in anxiety
2. 5HT₁A  active
   5HT₂A  in fear behavior
   5HT₃
3. Increased 5HT metabolism in anxiety - 5HT metabolites are found in urine and brain tissue

4. ANGER AND ANXIETY
   5HT₂C  receptor subtypes
   5HT₂A

5. 5HT₂ receptors are more super sensitive in ANXIETY DISORDERS

6. 5HT₁ receptor partial agonists - BUSPIRONE
   5HT₂ antagonists – NEFRAZODONE

7. Hypoactivity of 5HT receptors or hypoactivity are being currently investigated

D. NEUROPEPTIDES
1. Neuropeptides associated with normal anxiety reactions
2. Cholecystokinin (CCK)
   a. most abundant and widely distributed peptide NT in brain
   b. high densities in the hypothalamus, limbic system, basal ganglia, hippocampus, cortex and brain stem (all fear circuits)
   c. antagonists CCK-B for anxiety treatment

E. CORTICOTROPIN – RELEASING FACTOR

1. CRF
   a. widely distributed in brain
   b. highest concentrations in the hypothalamus
   c. secreted by the parvicellular neurons of the hypothalamic paraventricular nucleus
   d. receptors are most dense in neocortical, cerebellar and limbic structures (CRF-1 receptors)
   e. (CRF-2 receptors) subcortical lateral septum and hypothalamus
      1. CRF-2 alpha – brain
         CRF-2 beta – CNS and peripheral areas
   f. stress elevates CRF synthesis
   g. increased CRF
1. increased heart rate
2. mean arterial pressure
3. reduction of eating
4. fear conditioning
5. elevated in OCD patients and PTSD
6. not elevated in Panic Disorders

F. STRESS MODEL

1. May activate CRF in the region of the locus ceruleus
2. Activates NE in forebrain terminal projections
3. Stimulates release of CRF
4. Freed-Forward System - "Kindling" triggered by chronic stress

G. GLUTAMATE

1. Glutamate receptors mediate excitatory neurotransmission in the brain
2. Active in hippocampus for memory (long-term potentiation)
3. Stress activates cortical and limbic glutaminergic systems
4. NMDA antagonists and Glycine-B partial agonists reduce anxiety
5. Lamotrigine – reduces glutamate release
6. Metabotropic agonists for anxiety

H. DRUG TREATMENT FOR ANXIETY

1. Benzodiazepines

   a) Alprazolam – most often used for acute and long-term use in GAD (somatic symptoms)

   b) drugs that target 5HT and NE may be more effective for psychic anxiety symptoms

   c) risks of Benzo’s

      1. sedation
      2. memory disruption
      3. addictive
      4. withdrawal symptom rebound
      5. must taper drug slowly
      6. use drug with long half-life for tapering

   d) Benzo’s became second-line treatment or augmentation in 1990’s

   e) Non-Benzodiazepine-antianxiety agents

      1. Diphenhydramine (Benadryl)
      2. Hydroxyzine (Vistaril) FDA (Atarax)
      3. Meprobamate (Equanil) FDA (Miltown)
      4. B-Blocker (Propranolol) Inderal
      5. Venlafaxine (Effxor-XR) FDA (Antidepressant)
Buspirone (Buspar) FDA

2. Combination Therapy for Anxiety

   1. Two agents: AD with Benzo or hypnotic

3. Serotonergic Anxiolytics

   a. Buspirone (Buspar)  5HT₁A partial agonist

      1. does not interact with alcohol
      2. no withdrawal
      3. no dependence
      4. can be used with substance dependent individuals
      5. delay of onset like AD’s
      6. Benzo’s do not require adaption of receptors
      7. indicated for: elderly substance abuse, chronic anxiety
      8. can be used to augment AD’s

4. Noradrenergic Anxiolytics

   a. alpha-2 agonists to reduce NE release “STEP ON THE BRAKE”

   b. Ex: Clonidine
      alpha-2 agonist
      (will reduce physiological effects of anxiety) ex: reduce tachycardia, dilated pupils, sweating) *BUT NOT PSYCHIC OR EMOTIONAL

   c. Beta-Blockers - social phobia
5. **GABAergic Neurons and Benzodiazepine Anxiolytics**

a. GABA-A
   fast

b. synthesized from precursor Glutamate

c. enzyme used is glutamic acid decarboxylase (Glu-AD)

d. GABA$_A$ uses reuptake pump chloride channel
   Allosterically modulated by nearby Benzo receptors
   Nonbenzodiazepines sedative hypnotics and alcohol

e. GABA$_A$ receptors mediate alcohol effects, muscle
   relaxations, anticonvulsant effects

f. GABA$_B$
   1. Not allosterically modulated to Benzo's
   2. Will bind to muscle relaxant Baclofen
   2. Not linked to anxiety

g. GABA Receptors – five subtypes

   1. Omega 1
      Cerebellum
      Anxiolytics
      Hypnotic-Sedative

   2. Omega 2
      Spinal Cord and striatum
      Mediate muscle relaxant actions
3. Benzodiazepine 3 – peripheral
   (Outside CNS)       kidney

   h. GABA – Benzo actions
      POSITIVE ALLOSTERIC

1. natural ligand in brain for Benzodiazepine receptor

2. modulation of GABA receptor complex

3. positive allosteric interaction with Benzo’s and GABA$_A$

4. mediates chloride ion channel (GABA binding to GABA$_A$ receptor with the simultaneous binding of Benzo to it’s benzodiazepine site)
   *allosteric “othersite” will increase the amplification of GABA’s ability to increase the conductance of chloride through the channel)

i. **BENZODIAZEPINE INVERSE AGONISTS**
   (opposite effect of agonist)

   a) create anxiety
   b) proconvulsant properties

j. **BENZODIAZEPINE PARTIAL AGONISTS**
   (can separate effects)

   a) reduce sedation, dependency, withdrawal
   b) decrease anxiety

k. Flumazenil - Benzodiazepine antagonist

   a) can reverse the inverse agonist
IV. TREATMENT USES FOR ANTIANXIETY AGENTS

A. BEZODIAZEPINES

1. short time periods (weeks to months)
2. use for short-term stabilization
3. combine with AD then taper off

B. BARBITUATES

1. sedating
2. increased dependency
3. overdose - lethality
4. no true anxiolytic effect

C. AJUNCTIVE TREATMENTS

1. sedation
2. no specific anxiolytic effect
3. include antihistamines, beta adrenergic blockers and alpha 2 blockers (clonidine)

D. NEW AGENTS

1. partial agonists of GABA
2. cholecystokinin (CCK) antagonists
3. CRF antagonists

4. neuroactive steroids

E. INSOMNIA

1. primary

2. secondary

3. treatment
   a. sedative hypnotic drugs
   b. treating underlying disorders

4. classification of insomnia
   a. primary insomnia- underlying pathophysiology of sleep
   b. insomnia secondary to psychiatric disorder
   c. insomnia secondary to a medication or drug of abuse
   d. insomnia secondary to medical condition – (sleep apnea)
   e. circadian rhythm disturbance
   f. periodic limb movement disorder
   g. restless leg syndrome
G. SEDATIVE – HYPNOTICS

1. first-line treatment for insomnia
2. pharmacodynamics improved
3. mode of action improved
4. Zalepon (Sonata)
   Zolpidem (Ambien)

   a) act at selective omega 1 sites
      (benzodiazepine receptors)
   b) not at omega 2 receptors in brain – do
      not affect cognition, memory, motor
      functioning
   c) sedate
   d) rapid onset
   e) short duration
   f) triazolam (Halcion) is a fast-onset, short
      duration benzodiazepine that binds to
      GABA postsynaptic receptors
   g) nonbenzodiazepines may have partial
      agonist properties
   h) no rebound insomnia, dependence or
      withdrawal
   i) do not lose efficacy as Benzo’s can
   j) Zalepon (Sonata)

   1. rapid onset (1 hour peak levels)
   2. short duration
   3. better for sleep onset difficulty
   4. does not interfere with natural sleep
   5. middle nocturnal awakening – can
      take repeat dose
   6. no active metabolite
k) Zolpiden (Ambien)
   1. first omega 1 selective nonbenzodiazepine sedative hypnotic
   2. longer peak levels (2 to 3 hours)
   3. longer half-life (1.5-3 hours half-life)

l) Sedative-hypnotic benzos

   1. all benzo's are sedating
   2. shorter half-life best for insomnia
   3. difficulty with sleep onset
      a. use fast onset short acting agent
         ex: Alprazolam (Xanax)
         Lorazepam (Activan)
   4. middle-of-the-night insomnia
      a. intermediate-onset
         intermediate half-life
         ex: Lorazepam (Ativan)

   5. both onset and sleep maintenance use
      a. fast onset
         intermediate agent
         Triazolam – 15-30 min onset
         Ex: Oxazepam (Serax) 6-7 hours duration

m) Antidepressants with sedative-hypnotic properties

   1. TCA's
   2. Trazodone
      a. 5HT₂A antagonist
      b. induce and restore slow wave sleep
      c. can be combined with SSRI and given at night
3. Mirtazapine
   Nefrazodone
   *Both are 5HT₂A antagonists

n) Sedative-Hypnotics (other)

1. chloral hydrate (caution hepatic enzymes)
2. ethchlorvynol
3. piperidinedione derivatives

DRUG TREATMENTS FOR OBSESSIVE COMPULSIVE DISORDER, PANIC DISORDER & PHOBIC DISORDERS

I. OCD
   A. Criteria
      1. chronic psychiatric condition
      2. often emerges in childhood
      3. recurring obsessions (thoughts)
      4. compulsions (behaviors)
      5. must interfere with work, activities or relationships
      6. 2/3 of OCD patients obsess about dirt, contamination and germs
      7. 1/3 safety issues, checking behaviors
      8. 2/3 of OCD patients also experience major depression
      9. not care – 1 out of 50 adults
         1 of 200 children
      10.7% in first degree relatives

   B. Biology
      1. familial
      2. SSRI's are effective due to increased 5HT activity in basal ganglia, cingulated gyrus and prefrontal cortex
3. increased activation in prefrontal cortex and basal ganglia in OCD
4. abnormal activity normalizes with antidepressants treatment
5. theory – frontal lobe inhibition is abnormal in OCD
6. neural loop of thalamus – caudate and frontal lobe fails to inhibit itself
7. the caudate (basal ganglia) is richly innervated by 5HT neurons
8. 5HT inhibits the excessive metabolic activity – shuts down the maladaptive loop – OCD symptoms diminish
9. improvement in OCD linked to 5-HIAA (5-hydroxyindoleacetic acid) and platelet serotonin concentrations
10. 40% of OCD do not respond to SSRI’s
11. Dopamine dysregulation in Basal Ganglia – Tourette Syndrome (multiple motor and vocal tics)
12. 45-90% of Tourette patients have OCD
13. antidepressants (DA receptor antagonists help OCD) *can be added as adjunct to SSRI
14. atypical antidepressants – both serotonin-dopamine antagonists

C. Anatomy

1. (PET) Positron Emission Tomography projections from the orbitofrontal – medial prefrontal cortex to Basal Ganglia – OCD
D. Treatment

1. SSRI's – Luvox
2. TCA – *Clomipramine*
   a. unique anti-OCD independent of antidepressant effects
3. Depression with OCD – more 5HT involvement
4. higher doses are needed for OCD – SSRI’s later delay of effect (6-12 weeks) depression (4 to 8 weeks)
5. OCD does not remit 35% reduction in symptoms after 12 weeks of treatment
6. combinations
   a. SSRI + BENZO (CLONAZEPAM)
   b. SSRI + NON-BENZO (ZALEPON OR ZOLPIDEM)
   c. SSRI + ATYPICAL ANTIPSYCHOTIC
   d. SSRI + BEHAVIORAL THERAPY

II. PANIC ATTACKS AND PANIC DISORDERS

A. PANIC ATTACKS

1. *unexpected* terror
2. physiological arousal
3. sense of impending doom
4. lead to avoidance behaviors
5. can occur during sleep

B. PANIC DISORDERS

1. *recurrent* unexpected panic attacks
2. 1 month period of persistent anxiety related to attacks
3. 2% of population
4. usually begins in late adolescence or early adulthood
5. 2X rate in women
6. relatives 15-20%
7. 40% rate for monozygotic twins
8. suicide rate comparable to major depression

C. BIOLOGY OF PANIC

1. initial excess of NE
2. hypersensitive to alpha-2 antagonists
3. hyposensitive to alpha-2 agonists
4. ex: YOHIMBINE (alpha-2 antagonist promotes NE release)
   “cuts the brake cable” of the presynaptic NE autoreceptor (causes panic attacks in patients with panic disorder)
5. caffeine is an adenosine antagonist – synergic with NE
6. can trigger panic in Panic Disorder individuals, NOT in normals
7. Panic patients have less response to postsynaptic adrenergic agonists

D. GABA (GAMMA AMINOBUTYRIC ACID) IN PANIC DISORDER

1. allosteric modulation by Benzo’s is dysregulated
2. endogenous benzodiazepines may be dysregulated
3. benzodiazepines receptor sensitivity
4. brain may be producing an excess of anxiogenic inverse agonists
5. chloride channels conductance may be diminished due to reduced sensitivity of Benzo receptor site

E. (CCK) CHOLECYSTOKININ

1. increase CCK receptor sensitivity linked to panic

F. RESPIRATORY HYPOTHESIS

1. carbon dioxide hypersensitivity
2. lactate insensitivity
3. Panic patients may hyperventilate

G. FALSE SUCCATION ALARM THEORY

1. Brainstem-monitor for suffocation (supersensitive)
2. Oddin's Curse – congenital central hypoventilation syndrome --insensitive for suffocation

H. NEUROANATOMIC FINDINGS

1. PET-projections to hippocampus may be abnormal
2. LOCUS COERULEUS – central to modulation of vigilance, attention, anxiety and fear
3. hypersensitivity of the limbic system
4. PET- hemispheric asymmetry of parahippocampal blood flow
5. there are neuroadrenergic projections to hippocampus as well as raphe – may be dysregulated
I. TREATMENTS

1. SSRI’s – all are equally effective 3 to 8 weeks
2. Panic patients are more sensitive to SSRI’s than depressed patients – doses need to be started slower
3. start low – go slow!
4. doses are increased to the same or greater levels as AD’s over time

J. NEWER ANTIDEPRESSANTS

1. Nefrazodone (SERZONE)
2. Venlafaxine (EFFEXOR)
3. Mirtazapine (REMREON)
4. Reoxetine
5. Bupropion (WELLBUTRIN)

K. TRICYCLIC ANTIDEPRESSANTS

1. Imipramine
2. Clomipramine – second line
3. Desipramine
4. Doxepin
5. Amitriptyline
6. Nortriptyline

*5 and 6 are third line agents

L. MAO INHIBITORS

1. RIMAs may be less effective than the irreversible
M. **BENZODIAZEPINES**

1. adjunctive to SSRI’s due to delayed SSRI effect

2. disadvantages of Benzodiazepines include sedation, cognitive clouding, alcohol interaction, physiological dependence, withdrawal effects

3. high potency benzodiazepines
   (alprazolam) - Xanax
   (clonazepam) – Kolopin – better for panic than low-potency benzo’s (diazepam, lorazepam)

4. *slowly* discontinue Benzo

5. adding 5HT₂A antagonist (ex: trazodone) to an SSRI can augment efficacy of SSRI

6. panic disorder may need continued maintenance therapy

N. **NEW PROJECTS**

1. trials of Venlafaxine XR, Nefazodone, Mirtazapine

2. novel serotonergic agents
   a. 5HT₁A antagonists
   b. 5HT₁D antagonists
   c. neurokinin antagonists
   d. neuropeptide antagonists
III. PHOBIAS

A. **AGORAPHOBIA** – fear of leaving one’s home

B. **SPECIFIC PHOBIAS** – “simple phobias”
   Exposure to the feared situation or object causes immediate anxiety response or full-blown panic attack

C. **SOCIAL PHOBIA** – irrational fear of social or performance situations (associated with shyness, avoidant personality disorder to generalized social phobia)

D. **BIOLOGICAL BASIS OF SOCIAL PHOBIA**
   1. noradrenergic overactivity (tremor, tachycardia, and blushing)
   2. beta adrenergic blockers

E. **SOCIAL PHOBIA TREATMENTS**
   1. *PAXIL* – FDA approval (PAROXETINE)
   2. all five SSRI’s have proven effective (Paroxetine, Fluvoxamine, Fluoxetine, Sertraline and Citalopram)
   3. Venlafaxine, Nefrazodone
   4. third line MAO’s inhibitors

IV. **BIOLOGICAL BASIS**

   1. noradrenergic arousal system becomes overactive
   2. exaggerated startle response and autonomic hyperarousal
   3. hippocampus volume shrinks
   4. treatment:
      a. avoid benzodiazepines due to drug and alcohol abuse associated with PTSD