Learning Objectives

1. Differentiate among benzodiazepine and barbiturate classes regarding onset and duration of action, mechanisms of action, route of administration, termination of action and therapeutic indications
2. Describe advantages and disadvantages of benzodiazepine sedative hypnotics in comparison with barbiturates
3. Describe dangers in sedative therapy and treatment of overdose
4. Discuss potential for abuse of sedative-hypnotics and prevention and treatment of dependence

I. Sedative-Hypnotic Drugs: Overview

- Include benzodiazepines, barbiturates, alcohols (ethanol, chloral hydrate)
- Among the most widely prescribed drug classes
- High doses depress respiration; additive with other CNS depressants
- Chronic use can produce physical and psychological dependence

- General Depressants produce:
  - Sedation: decreases activity, modulates excitement, calms patient
  - Hypnosis (sleep): produce drowsiness and facilitate onset and maintenance of sleep; ideally want sleep state that resembles natural and from which patient can be easily aroused
  - All sedative hypnotics produce sleep at high doses

II. Mechanism of action: GABA<sub>Ａ</sub> Receptor

- GABA is the major inhibitory neurotransmitter in the CNS

- Therapeutic uses: anxiolytic, sleep-inducing; muscle relaxant, anticonvulsant
  - Therapeutic effects result from CNS actions
  - Dose-dependent CNS depression that varies by drug

  - Lowest dose: sedation
  - Highest dose: hypnosis, anesthesia, coma, death

- Biodisposition
  - Metabolized in the liver by P450 enzymes
  - Phase I (oxidation): many have active metabolites with long half-lives
  - Phase II (glucuronidation): excreted in urine
  - Pharmacokinetic properties differ for various benzodiazepines and affect their clinical use
  - Affected by hepatic function (disease, age, increased/decreased enzyme activity)

- Mechanism of action: GABA<sub>Ａ</sub> receptor
  - GABA receptor is also affected by general anesthetics, ethanol, inhaled drugs of abuse, allopregnanolone (metabolite of progesterone)
  - Ionotropic receptor composed of 5 subunits (pentamer) that assemble to form a Cl channel
  - Subunit diversity (8 classes with multiple isoforms = at least 18 subunits)
  - Isoforms have individual localizations in CNS
  - Receptor heterogeneity and in vivo data suggests that future drugs can be developed to target specific effects (i.e. anxiolytic but not sedating)

III. Classes

A. Benzodiazepines

1. Characterized based on elimination half lives
   - Short-acting (t<sub>1/2</sub> < 6 hrs): short-lived or no active metabolites
     - triazolam (Halcion®), midazolam (Versed®)
   - Intermediate-acting (t<sub>1/2</sub> 6-24 hrs): short-lived or no active metabolites
     - temazepam (Restoril), lorazepam (Ativan), estazolam (Prosom)
   - Long-acting (t<sub>1/2</sub> > 24 hrs): long-lived active metabolites
     - flurazepam (Dalmane®), diazepam (Valium®), quazepam (Doral)

2. Advantages over other sedative hypnotics
   - Safety: limited capacity to produce profound and fatal CNS depression
   - Less REM suppression
   - Less tolerance and enzyme induction
Benzodiazepine drugs

Anxiety:
- Alprazolam (Xanax) oral intermediate
- Chlordiazepoxide (Librium)
- Chlorazepate (Tranxene) short-acting
- Midazolam (Versed) short-acting

Anxiety, sedation:
- Diazepam (Valium) oral, i.v. long-acting
- Lorazepam (Ativan) oral, i.v. intermediate

Insomnia:
- Estazolam (Prosom) intermediate
- Flurazepam (Dalmane) oral long-acting
- Quazepam (Doral) long-acting
- Temazepam (Restoril) intermediate
- Triazolam (Halcion) oral short-acting

3. Mechanism:
- **Benzodiazepine (BZ) site**: potentiates GABA actions
  - BZ sites: BZ, BZ, BZ (also referred to as Omega, Omega, Omega)
  - Most benzodiazepines bind to all types of these sites, but zaleplon and zolpidem are BZ-selective
  - BZ site on the GABA-A receptor distinct from the GABA binding site
  - Benzodiazepines do not directly activate the receptor/channel, but increase the frequency of Cl− channel opening produced by submaximal concentrations of GABA
  - Safety probably results from binding properties: benzodiazepines do not have an effect on their own, but require GABA

4. Therapeutic Effects: CNS-mediated
- Anxiety: general anxiety and panic disorders
- Pre-Anesthetic (prep for surgery)
- Anesthesia: diazepam, midazolam are used i.v. during anesthesia as adjuncts, but do not produce anesthesia by themselves
- Anti-convulsant
- Muscle relaxation
- Alcohol Withdrawal Syndrome
- Sedative/sedation: i.e. diazepam, lorazepam, midazolam, produce muscle relaxation and anterograde amnesia
- Parenteral use associated with increased respiratory depression when used for conscious sedation: monitor respiration and cardiovascular function
- Parenteral diazepam can produce thrombophlebitis (due to vehicle for infusion: polypropylene glycol); midazolam is water soluble therefore doesn’t have this effect

5. Insomnia: want to decrease sleep latency with minimal “hangover”
- Sedative hypnotics usually decrease latency to sleep onset, increase duration of stage 2 REM, decrease the duration of REM and slow-wave sleep

Categories:
1. Transient insomnia: <3 days, usually emotional or situational stressor
   - Treatment: sleep hygiene, low dose hypnotics for 2-3 nights
   - Note: use prior to event (e.g. exam) may impair performance
2. Short-term insomnia 3 days-3 weeks, usually personal stressor
   - Treatment: sleep hygiene, adjunct hypnotic therapy (7-10 nights intermittently)
3. Long-term insomnia >3 weeks, no specific stressor
   - Treatment: sleep hygiene, exercise, relaxation training, behavioral modification
   - Pharmacological: disadvantages tolerance, rebound insomnia after termination, alters sleep patterns
   - BZ: decrease slow wave non-REM and REM (less)
   - Barbiturates: decrease REM

Long-term treatment
- Side effects: BZ tolerance, next day confusion; may worsen sleep apnea
- BZ and newer drugs preferred due to greater therapeutic index, less toxicity/overdose, less effect on sleep patterns, less abuse potential
- Short half life: patients with sleep onset insomnia but without significant daytime anxiety (i.e. need to be effective all day)
- Long half life: patients with significant daytime anxiety who can tolerate some sedation
- To discontinue use after >2 weeks taper rather than withdraw
  - If using short half life BZ, switch to long half life BZ, then taper
  - May not have difficulty with zopiclone

b. Drug Classification
- **Agonist**: positive allosteric modulator that facilitates GABA actions by increasing Cl− conductance, shifts GABA concentration-response curve to left
  - Includes clinically useful benzodiazepines and endogenous agonist (“endozepines”)
    - Full agonist: produces maximal effect (i.e. diazepam)
    - Partial agonist: less than maximal effect (i.e. alpidem)
      - Produce anti-anxiety effects with less sedation
- **Inverse Agonist**: negative allosteric modulators of GABA receptor function that decrease Cl− conductance, shift GABA concentration-response curve to right
  - Example: β-carbolines
  - Produce seizures and anxiety
- **Antagonist**: flumazenil (Romazicon): has no effect on its own but blocks effects of agonist/inverse agonist

h. Estazolam (Prosom) intermediate
5. Adverse Effects/Toxicity (may be increased in elderly)

A. CNS depression: residual sedation, fatigue, drowsiness, confusion, ataxia
Anterograde amnesia: parenteral benzodiazepines (i.e. diazepam, midazolam); oral triazolam has increased likelihood; flunitrazepam (Rohypnol)
Potentiates effects of other CNS depressants esp. problem with ETOH
Impair driving and psychomotor skills
Paradoxical Stimulation: talkativeness, anxiety, nightmares, tremulousness, hyperactivity, muscle spasms; more common in psychiatric patients

B. Respiration:
hypnotic doses of benzodiazepines don't depress respiration, although higher doses may have some effect. Care should be taken in children, those with impaired liver or lung function; additive effects with other CNS depressants such as opioids or alcohol

C. Cardiovascular: minor in normal subjects; can decrease blood pressure and heart rate at pre-anesthetic doses

D. Visual System:
diplopia, nystagmus, blurred vision; contraindicated in narrow-angle glaucoma (may be used with wide-angle glaucoma: more common type)

E. Reproduction:
Sedative-hypnotics cross the placental barrier and are detectable in breast milk
1st trimester: congenital malformations
Pre-delivery: large doses may produce hypothermia, hypotonia and mild respiratory depression in neonate

6. Chronic Administration

a. Tolerance (decreased responsiveness to drug after repeated administration) occurs with sedative-hypnotics
< cross-tolerance to other CNS depressants

b. Dependence

- Psychological dependence: most sedative-hypnotics are schedule III or IV because of abuse liability due to anxiety, euphoria and disinhibition
- Physical dependence: chronic use of most sedative-hypnotics can lead to dependence, characterized by a withdrawal syndrome (increased anxiety, insomnia, and CNS excitability that can lead to convulsions)
  - abrupt withdrawal may produce irritability, dysphoria, tremors, anxiety, dizziness esp. after sudden withdrawal
  - to avoid withdrawal, taper dose

7. Drug interactions:
- Additive depression with CNS depressants: alcohol, barbiturates, antipsychotics, antidepressants, opioids, antihistamines, anticonvulsant
- Cimetidine (Tagamet): inhibits metabolism of BZ
- Antagonist: flumazenil (Romazicon)
- Smoking may decrease the effect of benzodiazepines (tar stim hepatic enzymes)
- Benzodiazepines may
  - decrease the effect of levodopa
  - increase the effect of digoxin, phenytoin, probenecid

B. Novel benzodiazepine receptor agonists
- structurally unrelated to benzodiazepines but bind to BZ binding site

1. Classes
   a. zaleplon (Sonata)
      - BZ (omega-1) selective
      - Used for short term management of insomnia
      - Less risk of tolerance and dependence than benzodiazepines
      - Side Effects: headache, drowsiness, dizziness
      - Fast onset: 11/2 - 2 hrs; effects last ~8hrs
   b. zaleplon (Sonata)
      - BZ (omega-1) selective
      - Decreases sleep latency but has little effect on sleep time or architecture
      - Rapid onset and short duration of action (11/2 - 1 hr); can use multiple doses
   c. zaleplon (not in US)

C. Barbiturates
- "Due to their relative safety, benzodiazepines have largely replaced older sedative-hypnotics (i.e. barbiturates)
- Barbiturates: lack specificity in CNS, lower therapeutic index, frequent tolerance, greater abuse liability, more drug interactions, no antagonist
  1. Classes
     a. ultrashort: <60 min
        - thiopental (Pentothal), methohexital (Brevital®)
        - used as i.v. anesthetic
     b. short to intermediate
        - secobarbital (Seconal®), pentobarbital (Nembutal®)
        - oral or i.v. sedative hypnotic
     c. long-acting
        - phenobarbital, mephobarbital (Mebaral®), barbital
  2. Mechanism: facilitate GABA actions by increasing duration of channel opening
     - High doses may also directly open the channel
     - Promote BZ binding
     - Distinct from GABA and BZ sites
     - May also depress actions of excitatory neurotransmitters esp. glutamate (AMPA receptors)
     - Therefore: overall effect to enhance inhibition and decrease excitability
3. Pharmacological effects and clinical use
   a. anesthesia (thiopental, methohexital)
   b. anticonvulsant
   c. sedative-analgesic combinations
      • sedatives do not produce analgesia, therefore may need combination
      • Fiorinal (butalbital/acetaminophen/caffeine)
      • Fiorinal #3 (butalbital/tylenol #3 (acetaminophen, codeine))
   d. antagonize stimulant effects (ephedrine, dextroamphetamine, theophylline)
   e. sedative/hypnotic withdrawal (phenobarbital)

4. Factors affecting barbiturate action
   a. lipid solubility (ultrashort > short > long)
   b. interference with metabolism and excretion
   c. drug interactions
      1. additive with other CNS depressants
      2. enzyme induction

5. Acute toxicity and treatment of overdose (often deliberate)
   usually occurs at ~10X hypnotic dose (lower with ethanol)
   a. dialysis: remove drug
   b. supportive: maintain respiration, pH and fluid balance, body temp.

6. Tolerance
   a. 3-4 fold for hypnosis, less for lethality
   b. cross dependence with other sedative hypnotics
   c. pharmacodynamic (major) and pharmacokinetic (minor)
   d. more tolerance two sedative and hypnotic effects than anticonvulsant and lethal effects (i.e. therapeutic index decreases with tolerance)

7. Dependence and withdrawal
   a. withdrawal: excitability, convulsions, delirium
   b. cross abuse potential

8. Contraindications
   a. hepatic porphyria (defect in hemoglobin breakdown)
   b. pulmonary disease
   c. sensitivity

9. Drug interactions
   a. CNS depression: most commonly ethanol
   b. enzyme induction

D. Miscellaneous agents that resemble short-acting barbiturates
   1. Chloral hydrate (Noctec®, Somnos®): active metabolite trichloroethanol
   2. Paraldehyde: treat delirium tremens in hospitalized patients
   3. Meprobamate (Miltown, others): approved for anxiety, also used as night time sedative
      a. more similar to BZ, but greater abuse potential, decreased antianxiety effects
      b. large doses: severe or fatal respiratory depression, hypotension, shock, heart failure
      c. meprobamate is a metabolite of carisoprodal (Soma)
   4. Methaqualone (Quaalude®)
   5. Ethchlorvynol (Placidyl): short term treatment of insomnia
   6. Bromide: first sedative-hypnotic agent (mid 19th century)

E. Misc. agents of lower efficacy
   1. Antihistamines, Anticholinergics
      a. less reliable as hypnotic
   2. Melatonin: natural hormone, mild efficacy for sleep disorders and jet lag
   3. Valerian, Kava kava: herbal product with sedative activity