SUBSTANCE ABUSE: Sedative-Hypnotics/Alcohol Withdrawal
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OBJECTIVES
1. Describe the pharmacology and pathophysiology of sedative-hypnotic agents.
2. Be able to recognize the clinical manifestations of sedative-hypnotic intoxication.
3. Be familiar with some of the street drug names associated with sedative-hypnotics.
4. Identify potential pharmacotherapeutic and non-pharmacotherapeutic interventions used for the treatment of the sedative-hypnotic intoxication.
5. Identify potential pharmacotherapeutic interventions used for the treatment of the withdrawal from sedative-hypnotics.
6. Be able to recognize the clinical manifestations of acute alcohol withdrawal and the time course with which the typical phases of alcohol withdrawal occur.
7. Identify potential pharmacotherapeutic interventions used for the treatment of alcohol withdrawal.

SEDATIVE/HYPNOTICS

I. AVAILABLE FORMS

<table>
<thead>
<tr>
<th>BENZODIAZEPINES</th>
<th>BARBITURATES</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam (Valium)</td>
<td>Phenobarbital (Purple Hearts, Goof balls)</td>
<td>Methaqualone (Quaaludes)</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>Secobarbital (Reds, Red Devils, Red Birds)</td>
<td>Chloral Hydrate</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>Pentobarbital (Yellow Jackets)</td>
<td>Glutethimide</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>Amobarbital (Blue Heavens)</td>
<td>Ethchlorvynol</td>
</tr>
<tr>
<td>Flunitrazepam (Rohypnol; “date rape drug”; “Mexican Valium”, “rophies”, “rope”, “wolfies”)</td>
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</table>

II. PHARMACOLOGY

Benzodiazepines
Enhance the action of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) resulting in the generalized depression of the spinal reflexes.

Barbiturates
Depression of neuronal activity in the CNS through enhanced GABA-mediated synaptic inhibition. Hypotension occurs with large doses via depression of central sympathetic tone as well as by direct depression of cardiac contractility.

III. RANGE OF TOXICITY

Benzodiazepines
One of the most frequent causes of acute overdose, yet, there are very few well-documented cases of pure benzodiazepine-related deaths. *A lethal dose has not been established for any of the benzodiazepines.*

Barbiturates
In general, toxicity is likely when the dose exceeds 5-10 times the hypnotic dose. The potentially fatal oral dose of the shorter acting agents (pentobarbital, secobarbital) is 2-3 grams, compared to 6-10 grams for phenobarbital.

Phenobarbital: Therapeutic serum conc: 14-40 mcg/ml Severe toxicity >70 mcg/ml
V. TOXICOLOGICAL EFFECTS

- CNS depression, loss of short term memory
- Respiratory depression
- Cardiovascular instability (i.e., hypotension)

Flunitrazepam, trade name Rohypnol, is a long-acting (8-hour) benzodiazepine that is gaining both local and international attention as a favored sedative of abuse among adolescents and adults. It is ten times stronger than diazepam and is typically used in combination with alcohol. Rohypnol is also known as the “date rape drug” due to its ability to produce disinhibition and marked short term memory loss, especially when combined with alcohol (Mickey Finn blackouts). Rohypnol is being illegally imported to the U.S. by drug runners in the original manufacturer’s blister packs from Mexican and South American sources. It sells for $5-$10 per pill and can be taken orally or crushed and snorted.

VI. DECONTAMINATION

A. Syrup of Ipecac: Due to CNS depressant effects, SOI, if used at all, should be reserved for use with longer acting agents and only if it can be given within a few minutes of the exposure.

B. Gastric Lavage: Should be performed if the patient presents within four hours of ingestion.

C. Activated Charcoal/Cathartic
   1. Initial dose 50-100 gm or 1-2 gm/kg body weight.
   2. Multi-dose activated charcoal has been shown to reduce the elimination half-life of phenobarbital which may be attributed to its enterohepatic recirculation.

VII. TREATMENT and MONITORING

A. Basic and Advanced Life Support
   1. ABCs (airway, breathing, and circulation)
   2. Establish IV access
   3. Oxygen and assisted or mechanical ventilation as required.
   4. Thiamine, Dextrose, and Naloxone in the unconscious patient.

B. Initial Monitoring Parameters
   2. Heart Monitor, cardiac rhythm
   3. Neurologic status
   4. Urine output; fluid status.
   5. Urine and serum drug screens.

C. Enhanced Elimination (only for use with PHENOBARBITAL INTOXICATION)
   1. Multiple Dose Activated Charcoal
      i. Has been shown to increase clearance by 280% and decrease length of coma.
      ii. Dosing Regimen
          a. 25-50 gm q 4 hours.
          b. Monitor for active bowel sounds and GI motility during course of treatment,
          c. 24 hours of MDAC is usually sufficient to drop phenobarbital concentrations to subtoxic levels.

   2. Urine Alkalization
      i. Maintaining good urine output with concurrent urine alkalization will increase the ionized fraction of phenobarbital in the renal tubular fluid, thereby reducing its reabsorption and enhancing phenobarbital elimination.
      ii. Goal is to maintain urine pH of 7.5-8.0 utilizing sodium bicarbonate in the IV fluids.
      iii. Must have adequate potassium stores in order to achieve urine alkalization.

   3. Hemodialysis
      i. Reserved for cases where supportive measures fail to correct severe acid-base or electrolyte disturbances, hypothermia, or hypotension.
      ii. Advantage of being able to correct electrolyte imbalances.
4. Hemoperfusion
   i. Gives the greatest increase in elimination (2-4 times greater than dialysis) due to removal of
      protein bound drug as well as free drug.
   ii. Unable to correct electrolyte disturbances
   iii. Problems with platelet consumption, hypothermia, hypotension, and hypocalcemia.

D. FLUMAZENIL
   • Flumazenil (Romazicon) is a relatively new benzodiazepine receptor antagonist which may be used to
     reverse severe benzodiazepine intoxication.

DOSE:
   • Initial dose of 0.2 mg IV over 30 sec. Wait an additional 30 sec and if no response, give 0.3 mg over
     30 sec.
   • can give additional doses of 0.5 mg over 30 sec at 60 sec intervals up to 3.0 mg. Patients that respond
     to 3.0 mg can be titrated up to 5.0 mg.
   • no response within 5 min after a total dose of 5.0 mg suggests other causes.
   • may repeat treatment at 20 min intervals if re-sedation occurs. Can give up to 1 mg (given at 0.5
     mg/min) at any one time and up to 3 mg an hour.

CONTRAINDICATIONS TO USING FLUMAZENIL:
   • Any underlying illness or drug intoxication that may predispose patient to developing seizures. (e.g.,
     epilepsy, cocaine o/d, cyclic antidepressant o/d)
   • Patients at high risk for alcohol, benzodiazepine, or barbiturate withdrawal.
   • Increased intracranial pressure.

NOTE: The indiscriminate use of flumazenil in unresponsive patients who present without a reliable medical
history should be avoided due to the inability to rule coingestants such as cyclic antidepressants or
medical disorders that predispose the patient to suffering from seizures.

Sedative/Hypnotic Withdrawal

Signs and Symptoms
   • Severe anxiety, fatigue, irritability
   • Dysphoria, sleep disturbance
   • Onset and Course:
     Shorter half-life: -Onset 1-2 days -Duration 5-10 days.
     e.g., Triazolam, alprazolam, lorazepam, secobarbital, amobarbital, pentobarbital
     Longer half-life: -Onset 2-7 days -Duration 10-16 days.
     e.g., chlordiazepoxide, diazepam, flurazepam, phenobarbital

Risk Factors for Development of Withdrawal
   - length of use (generally > 3 months)
   - agents with shorter half-lives have a greater abuse potential and more severe withdrawal reactions.
   - rate of drug discontinuation.

Treatment of Sedative/Hypnotic Withdrawal
   • Utilize longer acting agents to provide a more gradual decline in serum concentrations. This degree of self-tapering
     may serve to blunt the severity of withdrawal reactions.
BARBITURATES  
**Phenobarbital load 120 mg every 1 to 2 hours** until the patient shows signs of mild toxicity: nystagmus, drowsiness, ataxia, dysarthria, and emotional lability. Patients requiring less than 480 mg are probably not barbiturate dependent. After loading, the patient is observed while the drug concentrations slowly decline over the next several days. The patient must be closely observed for respiratory depression.

BENZODIAZEPINES  
Switch patient to diazepam in a dose equivalent to the patient's previous daily maintenance dose. Develop a tapering schedule over a period of 4 to 8 weeks.

### Benzodiazepine Dosing Equivalency

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Dosage (mg)</th>
<th>Benzodiazepine</th>
<th>Dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>25</td>
<td>Flurazepam</td>
<td>15</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>2</td>
<td>Lorazepam</td>
<td>1</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5</td>
<td>Triazolam</td>
<td>0.5</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>30</td>
<td>Alprazolam</td>
<td>0.25</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>2</td>
<td>Chlorazepate</td>
<td>3.75</td>
</tr>
</tbody>
</table>

ALCOHOL WITHDRAWAL

**Ethanol-Pharmacology**

- Tolerance and physical dependence of ethanol are believed to be manifestations of the body’s compensatory neurophysiologic changes to off-set the depressant effect of alcohol on neuronal excitability, impulse conduction and neurotransmitter release. When alcohol ingestion is abruptly stopped or rapidly decreased, the compensatory changes give rise to the signs and symptoms of the withdrawal reaction.

**Pathophysiology of Alcohol Withdrawal**

- When an alcohol dependent person stops his intake of ethanol in an abrupt and sustained manner, the compensatory CNS mechanisms that have developed over months and years of daily drinking to counteract alcohol’s depressant effects start to take over resulting in a hyperadrenergic state of intense sympathetic autonomic stimulation. This hyperadrenergic state results in hypertension, tachycardia, tachypnea, tremors, diaphoresis, and anxiety.
- Other features suggest an increased propensity for seizures and psychotic behavior sometimes manifested as hallucinations.
- The severity of the withdrawal varies from individual to individual and is dependent on the intensity and duration of the preceding alcohol abuse.
- Alcohol withdrawal syndrome becomes progressively more severe with increasing years of heavy daily alcohol abuse irrespective of age.

<table>
<thead>
<tr>
<th>Hours after the cessation or reduction in alcohol consumption</th>
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</thead>
<tbody>
<tr>
<td><strong>ONSET</strong></td>
</tr>
<tr>
<td><strong>PEAK</strong></td>
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<tr>
<td><strong>DURATION</strong></td>
</tr>
</tbody>
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**KINDLING PHENOMENA**: repeated subthreshold stimulation of the CNS during alcohol withdrawal causes an increased sensitivity and excitatory neuronal response. This neuronal response increases with each episode of withdrawal and may eventually lead to seizures or severe complications. Inadequate benzodiazepine therapy early on in the patient’s clinical course of alcohol abuse and withdrawal may subsequently produce withdrawal episodes of increasing severity.2-5
**Clinical Manifestations of Alcohol Withdrawal**

<table>
<thead>
<tr>
<th>Minor Withdrawal</th>
<th>Major Withdrawal</th>
<th>Seizure Activity</th>
<th>Delirium Tremens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• tremors (75-80%)</td>
<td>• visual and infrequently auditory hallucinations</td>
<td>• usually precede DTs</td>
<td>• Gross tremor</td>
</tr>
<tr>
<td>• irritability</td>
<td>• fever</td>
<td>• grand mal</td>
<td>• visual hallucinations</td>
</tr>
<tr>
<td>• anorexia</td>
<td>• disorientation</td>
<td>• occur in first 24-48 hours</td>
<td>• profound confusion</td>
</tr>
<tr>
<td>• nausea</td>
<td>• incontinence</td>
<td>• require little or no anti-convulsant therapy</td>
<td>• mydriasis</td>
</tr>
<tr>
<td>• vomiting</td>
<td></td>
<td></td>
<td>• markedly increased autonomic activity</td>
</tr>
<tr>
<td>• insomnia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mild to moderate increases in HR and BP</td>
<td>• marked hyperactivity and potentially life-threatening elevations in vital signs</td>
<td>Seizure Characterized by:</td>
<td>• 5% of hospitalized alcohol withdrawal patients will experience true DTs</td>
</tr>
<tr>
<td></td>
<td>• Seizures occur in 7% of individuals due to a reduction in seizure threshold and are associated with a 28% risk of progressing to DTs without adequate treatment.</td>
<td>• short post-ictal period</td>
<td>• Mortality may be as high as 15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• absence of incontinence or tongue biting</td>
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</table>

**Risk Factors**
The severity and onset of alcohol withdrawal can be predicted with reasonable certainty by considering the following factors. Patients with 0-2 of these factors are at low risk for severe withdrawal, 3-6, moderate risk, and 7-9, high risk.

- age over 40
- male gender
- daily consumption equivalent to one fifth hard liquor
- drinks around the clock to maintain a steady alcohol level
- excessive drinking for more than 10 years
- development of tremulousness and anxiety within 6 to 8 hours
- history of seizures, hallucinations, delusions, with alcohol withdrawal
- presence of an acute medical problem such as pneumonia
- alcohol level of 300 mg/dl or greater on admission

**Treatment**
- Benzodiazepines are the drugs of choice for the treatment of alcohol withdrawal as well as prevention in those patients at high risk for withdrawal.
- The mechanism as to how a benzodiazepine may attenuate the autonomic hyperactivity seen with alcohol withdrawal has not been clearly elucidated.

**BENZODIAZEPINES:** Drug of choice for the treatment of alcohol withdrawal

A. Mechanism of Action
• Classified as a sedative-hypnotic but in higher doses may have some effect on the noradrenergic and hypothalamic-pituitary-adrenal axis to diminish the symptoms of withdrawal (tachycardia, hypertension and diaphoresis) caused by the hyperactive sympathetic nervous system.
• Anti-anxiety
• Anti-convulsant ---> may prevent the progression to seizures and DTs
• BZDs are not effective in relieving symptoms of disorientation and hallucinations.

B. Indications
• All symptomatic patients!!
• Patients with a strong potential for withdrawal based on history may have prophylactic BZD therapy and undergo close monitoring.

C. BZD Selection
• Any BZD may be efficacious in the treatment of alcohol withdrawal provided appropriate dosing is employed. No differences in outcome other than costs have been shown in the medical literature.
• Agents with longer elimination half-lives and agents that are metabolized to active metabolites (e.g. Librium™ or diazepam) provide a more gradual decline in physiologic concentrations and pharmacological activity. These types of agents may provide a smoother more predictable control of withdrawal symptoms as the long elimination half-life and the formation of active metabolites create a self-tapering pharmacological effect.
• Ideally, the agent should have a rapid onset and have an intermediate elimination half-life.

*** Key factors to consider when selecting a benzodiazepine in the treatment of alcohol withdrawal.

1. **Hepatic Function:** Choice of the type of benzodiazepine to use in patients with suspected liver failure is debatable.
   • BZDs which are oxidatively metabolized (chlordiazepoxide, diazepam, clorazepate, triazolam, prazepam, alprazolam, and midazolam) may undergo a reduced rate of metabolism in patients with liver failure resulting in prolonged oversedation.
   • BZDs which are glucuronidated (lorazepam, oxazepam, temazepam) are less dependent on the liver for metabolism and therefore, may be more suitable for use in patients with evidence of liver failure.
   • A problem exists in that it is difficult to assess the degree to which a patient has liver failure such that drug metabolism may be impaired. Hepatic failure or even hepatic insufficiency cannot be definitively proven by laboratory findings. Currently, prothrombin time, total bilirubin and serum albumin are the most useful indicators of significant hepatic insufficiency and failure.

2. **Age:** Direct correlation between the elimination half-life of oxidatively metabolized benzodiazepines and age. Lorazepam is not affected by age.

3. **Cost:** 2 studies completed at Regions Hospital in St. Paul, Minnesota evaluated the treatment of alcohol withdrawal in patients< 60 years of age without evidence of hepatic failure.\textsuperscript{6,7} The findings are as follows:
   • **Study A:** BZD treatment during hospitalization (ranging from lorazepam or midazolam drips to intermittent bolus injections and oral therapy) demonstrated a mean BZD acquisition cost per patient of $1000 and duration of ICU stay of 4 days.
   • **Study B:** Conducted after the institution of a lorazepam or chlordiazepoxide intermittent injection protocol demonstrated a mean acquisition cost of BZD per patient of $50 and a reduction in ICU stay to 1 day!!!

D. Dosing Strategies
• **BZD Tapering Protocol / Front-End Loading WITH prn orders**
The major principle to follow in the use of these medications is to use high dosages in the first 24 to 48 hours with gradual tapering over the next three to four days.

**DIAZEPAM** (*Valium*)

1. **Front-end loading (symptomatic patients):** 5mg IV every 15-30 minutes until patient is calm and sedated.
   - Asymptomatic patients who are at a high risk for developing withdrawal need not receive front-end loading but should be started on a daily maintenance regimen.

2. **Initial Maintenance:** 5-10 mg IV or PO every 2 to 6 hours depending on the severity of the initial withdrawal. A gradual dosing taper is then scheduled over the following 3-4 days.
   - Another method for determining an appropriate maintenance regimen is to add up the cumulative doses of diazepam required to sedate the patient during front-end loading session. Take the cumulative front-end sedating dose and divide it up into four to 6 doses per 24 hour.
   - Let’s say for example a severely symptomatic patient receives diazepam 5mg IV X 18 doses over a three hour period as part of the front-end loading session in order to achieve sedation and abatement of his withdrawal symptoms. His maintenance regimen would then be 90 mg diazepam divided by 6 daily doses. His initial maintenance drug order would then be **15 mg po or IV q 4 hours**.
   - A prn (as needed) order must also be made along with the maintenance order in order to treat any “breakthrough” symptoms that may develop in between maintenance doses.
   - Scheduled doses prevent breakthrough symptoms
   - Must hold dose if patient oversedated
   - **Important to note that unusually large doses of BZDs may be required and that inadequate BZD dosing may produce withdrawal episodes of increasing severity.**

**LORAZEPAM** (*Ativan*)

- Utilized in those patients with significant liver dysfunction or ages > 60 to 65 years.

E. Adjunctive Therapy to Benzodiazepine Use

1. **Clonidine**
   - Effective for treatment of alcohol withdrawal induced hypertension and tachycardia.
   - May help promote sedation
   - Clonidine patches take 24-48 hours to reach therapeutic concentrations, therefore, acute oral therapy is required initially.
   - **DOSE:** 0.6 mg/day in 2-4 divided oral doses plus clonidine patch 0.2 mg/day

2. **Beta-Blockers**
   - Effective for treatment of alcohol withdrawal induced hypertension and tachycardia.
   - Useful for the treatment of tremors, palpitations and some behavioral signs of alcohol withdrawal.
   - May decrease hospital stay and BZD requirements.
   - Limited by their effects on vital signs and patient tolerability.
   - **DOSE:** Atenolol 50-100 mg/day, titrated to heart rate and blood pressure.

3. **Haloperidol**
   - Efficaceous and safe for use in severe agitation, hallucinations, and DTs
   - No adverse effects on seizure threshold with minimal effects on respiratory and hemodynamic function.
   - **DOSE:** No established therapeutic range
   - Initial dose of 2.5 mg IM/IV/PO (at less than 5 mg/min) q 4 hours.
   - May increase dose to 5-10 mg q 4 hours as needed.
   - Severe hallucinations and delirium may require repeat dosing every 30-60 minutes.
• Elderly patients or patients with hepatic dysfunction require smaller doses.
• If agitation persists, doubling the previous dose has been recommended.

G. Other Pharmacologic Considerations

1. Vitamins/Electrolytes
   • In general, a patient with a history of chronic alcohol abuse will have poor nutritional status.
   • Thiamine
   • Magnesium - hypomagnesemia may lower seizure threshold
   • Folic acid/ multivitamin supplements

2. Phenytoin
   • No evidence exists to support the prophylactic use of phenytoin in preventing the recurrence of alcohol withdrawal seizures.
   • Patients who are witnesses having alcohol withdrawal related seizures are treated with a BZD (diazepam or lorazepam) and phenytoin.

H. Patient Monitoring
   • Frequent checks of vital signs for alcohol withdrawal induced tachycardia, hypertension and hyperthermia.
   • Titrate BZD according to the calculated total daily dosage requirements for control of withdrawal signs and symptoms.
   • In severe DTs base dosage on vital signs and total hours of rest.
   • Hold scheduled doses if patient oversedated
   • Use flumazenil (BZD antagonist) is a relative contraindication in oversedated patients due to the risk of seizure precipitation.
   • Be alert to the fact that use of a beta-blocker or clonidine may cause problems with hypotension and bradycardia.
   • Monitor for hypotension and respiratory depression secondary to BZD intoxication.

REFERENCES

Sedative-Hypnotics

Alcohol Withdrawal

Substance Withdrawal