SUBSTANCE ABUSE: Opiates/Hallucinogens/ Gamma-hydroxybutyrate (GHB)/Inhalant Abuse
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OBJECTIVES
1. Describe the pharmacology and pathophysiology of opiate drugs, hallucinogens and GHB.
2. Be able to recognize the clinical manifestations of opiate, hallucinogen and GHB intoxication.
3. Be familiar with the some of the street drug names associated with the opiates, hallucinogens and GHB.
4. Identify potential pharmacotherapeutic and non-pharmacotherapeutic interventions used for the treatment of the opiate, hallucinogen and GHB intoxication.
5. Identify potential pharmacotherapeutic interventions used for the treatment of the withdrawal from opiates.
6. Understand the prevalence of inhalant abuse among young adolescents as well as the volatile substances commonly abused.
7. Describe the pharmacology and pathophysiology of some of the more common chemicals used by the volatile substance abuser.
8. Be able to recognize the clinical manifestations of intoxication with some of the more common chemicals used by the volatile substance abuser.

OPIATES

I. AVAILABLE FORMS

- Natural opium, morphine, and codeine are derived from the Poppy Plant (Papaver somniferum). This was the flowering plant that knocked out Dorothy and the Gang as they were running across the field of flowers toward the Wizard’s castle in the movie The Wizard of Oz.

<table>
<thead>
<tr>
<th>CHEMICAL NAMES</th>
<th>STREET DRUG NAMES OF NARCOTICS</th>
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<tbody>
<tr>
<td><strong>Natural Opiates</strong></td>
<td></td>
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<tr>
<td>Morphine, codeine</td>
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<tr>
<td>Opium; Hashish</td>
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<tr>
<td>Heroin</td>
<td>Percodan</td>
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<tr>
<td>Oxycodeone</td>
<td>Dilaudid</td>
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<td>Hydromorphone</td>
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<tr>
<td><strong>Synthetic</strong></td>
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<tr>
<td>Meperidine</td>
<td>Demerol</td>
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<tr>
<td>Methadone</td>
<td>Dolophine</td>
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<tr>
<td>Diphenoxylate</td>
<td>Lomotil</td>
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<tr>
<td>Fentanyl</td>
<td>Sublimaze, “China White”, “Tango and Cash”</td>
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<tr>
<td>Propoxyphene</td>
<td>Darvon, Darvocet (mixed with acetaminophen)</td>
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II. SOCIAL IMPACT

It is estimated that 4 to 6.5 million Americans have recently abused narcotics and 2.5 million citizens have used heroin at some time in their lives. Heroin-related emergency room visits also continue to increase annually. Unlike the stimulants, opiates induce a profound physical dependence in addition to a strong psychological dependence. The physical dependence in the regular user and subsequent withdrawal syndrome generally requires more extensive
medical intervention and makes drug rehabilitation much more difficult and costly. John Belushi, a famous actor/comedian, reportedly died following the injection of a “speedball” which is a combination of cocaine and heroin. Kurt Cobain, the leader of the famous rock-band Nirvana, committed suicide following his long battle with depression and heroin addiction.

III. PHARMACOLOGY

- Opiate agents exert their effects through the mu, kappa, sigma, delta, and epsilon endorphin receptors which in a naive person produce such classic effects as analgesia, sedation, euphoria, constipation (decreased bowel motility), and miosis. With chronic use, receptor tolerance develops leading to the escalation of doses to achieve the same desired effect and physical dependence.

IV. TOXICOLOGICAL EFFECTS

Classic Opiate Toxicity

- Consists primarily of CNS depression, respiratory depression, cardiovascular instability (i.e., hypotension), miosis, diminished bowel motility (constipation).

Seizures

- Seizure may occur with certain compounds [e.g., meperidine (Demerol), propoxyphene (Darvon)]. Patients chronically using meperidine, especially those with renal insufficiency, are at risk for developing normeperidine toxicity. Normeperidine toxicity is associated with tremor, myoclonus, or seizures. This type of neurotoxicity is not reversed with naloxone.
- Tramadol overdose has also been associated with the development of seizures. Naloxone administration is ineffective for tramadol-induced seizures and may even increase the risk of seizure development.

Serotonergic Excess (‘Serotonin Syndrome’)

- Meperidine, dextromethorphan, and tramadol all possess some serotonergic activity and all have been associated with the development of serotonin syndrome when taken with monoamine oxidase inhibitors. Serotonin syndrome is characterized by the development of intense muscle rigidity, tremors, severe hyperthermia, altered mental status, and death. It is also confused with or misdiagnosed as Neuroleptic Malignant Syndrome (NMS).
- Treatment is essentially supportive with emphasis placed on applying aggressive cooling measures and muscle relaxants to keep the body temperature down.

Cardiac Arrhythmias

- Intraventricular conduction delays, heart block, bigeminy, ventricular arrhythmia and non-specific ST-T wave abnormalities may result from propoxyphene overdose. Norpropoxyphene, a metabolite of propoxyphene is responsible for this cardiotoxicity which cannot be reversed with naloxone. The norpropoxyphene blocks fast sodium channels of the myocardium producing a membrane stabilizing or ‘quinidine-like’ effect similar to cocaine and the cyclic antidepressants.
- Aggressive intravenous sodium bicarbonate therapy in conjunction with lidocaine therapy should be employed with evidence of propoxyphene-induced cardiotoxicity.

Anticholinergic Toxicity

- Lomotil is a commonly used antidiarrheal preparation that contains diphenoxylate(an opiate) and atropine. Excessive dosing of Lomotil, especially in children, may lead to severe opiate intoxication due to the diphenoxylate and anticholinergic poisoning due to the atropine.

Pulmonary Edema

- Noncardiogenic pulmonary edema may occur, often after resuscitation and administration of the opiate antagonist, naloxone. The exact etiology of this complication is not well known.
Miscellaneous

- Abuse of dextromethorphan (DMX) in high doses (4 ounces of DM cough syrup) may produce an abuser ‘high’ similar to phencyclidine. Movement disorders, phencyclidine-like psychosis, CNS depression and respiratory depression have been associated with severe overdoses of dextromethorphan. Naloxone appears to reverse the CNS and respiratory depression.

V. TREATMENT AND MONITORING

- Consists primarily of supportive measures in combination with naloxone (Narcan), an opiate receptor antagonist.

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.

B. Oral Ingestion
   1. AC/C
   2. Serious opiate toxicity from ingestion is uncommon.

C. Initial Monitoring Parameters
   1. Vital Signs, heart monitor, cardiac rhythm
   3. Neurologic and Respiratory status
   4. Urine output; fluid status.
   5. Urine and serum drug screens.

D. Naloxone: Opiate receptor antagonist
   1. **DOSE:** 0.4 to 0.8 mg IV initially. Repeat dose every 2-3 minutes if there is no response, up to a total of 10-20 mg if opiate intoxication is strongly suspected.
   2. Keep in mind that, if one is too aggressive with the use of naloxone, they may precipitate symptoms of opiate withdrawal in opiate dependent individuals. In opiate dependent individuals, it is best to start out with small bolus dosing (0.8 mg to 1.0 mg) and titrate upward.
   3. The duration of naloxone (2-3 hours) is shorter than that of most of the opioids. Therefore, it is recommended that the intoxicated patient be observed for at least 3-4 hours after the last dose of naloxone to insure that the patient does not become “reintoxicated” once the effect of naloxone wears off.
   4. Naloxone administration is ineffective for seizures caused by normeperidine, tramadol, or propoxyphene toxicity and may even increase the risk of seizure development in some cases.
   5. Naloxone will not reverse propoxyphene-induced cardiotoxicity.

E. Alternative Opioid Antagonists
   1. **Nalmefene** (naloxone derivative)
      - Longer duration of action than naloxone
      - More difficult to titrate to effect than naloxone
      - Risk of more prolonged withdrawal symptoms
      - May be of some benefit over naloxone in cases of significant opioid intoxication where patients require constant re-administration of naloxone or a naloxone infusion.
      **DOSE:** 0.1 mg IV bolus initially; if no evidence of withdrawal, 0.5 mg IV can be given, followed by 1 mg in 2-5 minutes prn.
   2. Naltrexone
      - Much longer duration of action (24-48 hours) than naloxone or nalmefene.
      - Much more difficult to titrate to effect than naloxone
      - Generally not used to manage acute opiate intoxication due to the risk of precipitating a
prolonged withdrawal syndrome.

F. Propoxyphene-Induced Cardiotoxicity
   • Use sodium bicarbonate and lidocaine as first-line agents during ACLS to reverse the membrane stabilizing effects of propoxyphene.

G. Seizures
   • Treatment is symptomatic and supportive with the initial aggressive use of IV benzodiazepines.

VI. OPIATE ADDICTION

Opiates exhibit all the classic properties of an addictive drug (tolerance, dependence, and an abstinence syndrome on immediate withdrawal). Opioid agents exert their effects through the mu, kappa, sigma, delta, and epsilon endorphin receptors which in a naive person produce such classic effects as analgesia, sedation, euphoria, constipation, and miosis. With chronic use, receptor tolerance develops to its pharmacologic effects requiring a continuous escalation of doses to achieve the same desired effect. When these drugs are abruptly discontinued, or when a pure opioid antagonist such as naloxone or naltrexone is given, a predictable withdrawal syndrome occurs.

VII. CLINICAL MANIFESTATIONS OF OPIATE WITHDRAWAL

a. Onset:
   • Dependent on the quantity of drug abused, the frequency of use, and the elimination half-life of the abused agent(s).
   • **Opiate withdrawal is not life-threatening** unless the patient has a concurrent serious underlying illness such as cardiac disease.
   • Opiate withdrawal symptoms typically begin 6 to 8 hours after the last dosage for heroin abuse but may be delayed up to 36 to 72 hours after methadone abuse.
   • Opiate withdrawal will occur within minutes if an opiate dependent patient is given naloxone or another opioid antagonist. The indiscriminate use of naloxone in the field, emergency department, or in-patient hospital setting without taking into account an individual’s potential history of chronic opiate abuse may result in the rapid onset of severe withdrawal symptoms. Severe opiate withdrawal may compromise the initial medical care or even place the patient and medical personnel at risk for injury due to the violent behavior that may ensue during withdrawal in some individuals. Naloxone is still indicated in cases of severe opiate intoxication, especially if the patient is at risk for or is suffering from severe respiratory depression.

b. Signs and Symptoms of Withdrawal

<table>
<thead>
<tr>
<th>VOLUNTARY BEHAVIOR</th>
<th>INVOLUNTARY BEHAVIOR</th>
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<tbody>
<tr>
<td>Pleas, demands, manipulations, or even mimicking and exaggerating signs of withdrawal in an attempt to obtain their &quot;opiate fix&quot;.</td>
<td><strong>Initial S/SX:</strong></td>
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<tr>
<td>These patients often have an overwhelming fear of not being able to obtain their needed drug. It is not uncommon for them to present to hospitals feigning symptoms of serious illness that generally produce a large amount of pain (e.g. kidney stones) in order to be prescribed opiate analgesics.</td>
<td>• Restlessness, insomnia, yawning</td>
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<td></td>
<td>• Lacrimation, rhinorrhea, diaphoresis</td>
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<tr>
<td></td>
<td><strong>Latent S/SX:</strong></td>
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<tr>
<td></td>
<td>• Mydriasis, piloerection (&quot;gooseflesh&quot;)</td>
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<tr>
<td></td>
<td>• Myalgias, arthralgias, abdominal pain</td>
</tr>
<tr>
<td></td>
<td>• Tachycardia, hypertension, tachypnea</td>
</tr>
<tr>
<td></td>
<td>• Nausea, vomiting, diarrhea, dehydration</td>
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</table>
NOTE: Under most circumstances, opiate withdrawal does not require hospitalization. Although an individual may experience a number of uncomfortable symptoms, opiate withdrawal is not a potentially life-threatening syndrome such as alcohol or benzodiazepine withdrawal.

VII. TREATMENT

A. METHADONE

The abatement of opiate withdrawal may be achieved by the replacement of an opiate agent. Methadone is the preferred agent for opiate replacement because of its prolonged half-life and its ease of oral and parenteral administration.

Initial Intervention for Opiate Withdrawal:
- 5 to 20 mg of methadone IM is usually adequate for the acute management of severe opiate withdrawal.
- Titrate the methadone dose up from 5 mg to 20 mg every 6 hours until the objective withdrawal symptoms are alleviated.
- No attempt at opiate detoxification should be made for acute opiate withdrawal while the patient is in the hospital setting. Once the patient is stabilized, then attempts should be made to enroll the patient in a federally licensed methadone detoxification program.

Maintenance Therapy
- 40 to 80 mg of methadone orally per day with a plan for a gradual dosage taper is usually adequate to prevent opiate withdrawal in patients enrolled in a federally licensed methadone treatment program. The daily methadone dose may given as a single oral dose or divided into two daily doses.
- The detoxification period may range anywhere from 10 to 180 days. The standard detoxification period as defined by the FDA is 21 days. The method by which the methadone daily maintenance dose is tapered is highly patient specific. An initial approach may be to decrease the daily methadone dose by 10% every other day. For a methadone detoxification program to work, the patient must also undergo intense psychotherapy, counseling, and group therapy.

NOTE:
- Patients may be legally prescribed methadone as part of a long-term maintenance program for the treatment of opiate withdrawal only by a physician federally licensed to work in a methadone treatment program.
- Patients can receive methadone as part of a detoxification program for opiate dependency only if they have been enrolled in a federally licensed methadone treatment program.
- A physician that is not licensed to prescribe methadone in a methadone treatment program may prescribe methadone to manage opiate withdrawal in the hospitalized patient, but no attempts should be made to detoxify the patient in a hospital setting. No patient should be admitted for opiate withdrawal unless there are concerns about a separate underlying illness such as cardiac disease.
- Patient’s cannot be given methadone in an outpatient setting (this includes emergency departments) unless the outpatient setting is a licensed methadone treatment program.

B. BUPRENORPHINE/NALTREXONE

1. Mixed agonists-antagonists (buprenorphine) has been studied in the outpatient setting. Benefits include little physical dependence, long duration of action, and possibly better efficacy as compared to methadone. Needs more clinical evaluation.

2. Pure opiate antagonists (naltrexone) have been combined with clonidine with some success for the treatment of opiate dependence and withdrawal. The withdrawal symptoms appear to be more severe initially, but the duration of withdrawal is shorter. Naltrexone has also been utilized as an abstinence tool.
C. CLONIDINE

**Mechanism of action:** The locus ceruleus accounts for one-half of the noradrenergic inputs to the CNS and serves to orient the individual towards potentially threatening external stimuli. The mu opiate receptors act in an inhibitory fashion on the LC. Thus, opiate intoxication leads to a state of decreased vigilance or somnolence. Conversely, opiate withdrawal in chronic opiate abusers may produce a state of hyperactivity in the LC with increased secretion of norepinephrine by the LC. Clonidine is an alpha-2 adrenergic receptor agonist. Alpha-2 receptors are also located on the locus ceruleus (LC) and have inhibitory action on the firing of the LC. Thus, opiate withdrawal, which is manifested as a state of adrenergic hyperactivity of the LC, can be antagonized by clonidine through its action on the alpha-2 adrenergic receptors on the LC.

- Clonidine is not an opioid substitute or agonist. Clonidine acts to attenuate the signs and symptoms of autonomic hyperactivity associated with opiate withdrawal. Clonidine does not effectively reverse the anxiety, dysphoria, restlessness, insomnia, myalgias, arthralgias, and GI distress that may be seen with opiate withdrawal.

D. SUPPORTIVE MANAGEMENT OF THE OPIATE WITHDRAWAL

1. Promazine may be useful to manage both agitation and nausea/vomiting.
   - 25 mg IM q 30 minutes, prn up to a maximum of 125 mg.
2. Haloperidol or benzodiazepine sedation may also be useful to manage acute agitation.

MISCELLANEOUS COMPLICATIONS IN THE INTRAVENOUS DRUG ABUSER

a. **Vasculitis**, especially with the stimulants, can disrupt effective blood circulation to essential organs and predispose patient to thrombosis, emboli, and stroke.

b. Blood contamination, especially from shared needles, can result in vital hepatitis B and HIV infection.

b. Bacterial and foreign body contamination may result in endocarditis, tetanus, wound botulism at the injection site, osteomyelitis, and pulmonary and soft tissue abscesses.

c. All potential IV drug abusers should be evaluated for Hepatitis B and HIV as part of their initial medical work-up when ever they are seen at a medical institution.

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**HALLUCINOGENS**

- Lysergic acid diethylamide ("LSD" or "acid") is becoming a popular form of drug abuse among adolescents. Blotter acid is a common dosage form where the liquefied drug is applied to amusing cartoon stickers such as *Beavis and Butthead* or even *Mickey Mouse*. These stickers are then either placed under the tongue or applied as a tattoo sticker. Sugar cubes and candy cigarettes are also popular vehicles for carrying LSD for eventual ingestion.

- Deaths attributed to hallucinogens are rare, and are usually associated with accidents due to the user’s altered perception of reality.

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**Hallucinogens** | **Mechanisms of Toxicity and Clinical Effects**
| Lysergic acid diethylamide (LSD, “ACID”, “Purple Haze”) | Incompletely understood. LSD and other hallucinogens are believed to exert some of their effects through stimulation of central serotonin receptors resulting in euphoria followed by visual and auditory hallucinations, perceptual distortions, and affective disability. LSD is structurally similar to serotonin.  
  • Effects generally disappear after about 12 hours. "Flashbacks" may occur, sometimes years after the last exposure. |
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<tbody>
<tr>
<td>Psilocybin (“Magic mushrooms”, “Shrooms”)</td>
<td>Mechanism of toxicity is not well defined. Like LSD, psilocybin is structurally similar to serotonin. Clinically, psilocybin produces effects similar to LSD. Psilocybin sold on the streets is rarely authentic, but is usually edible mushrooms adulterated with LSD.</td>
</tr>
<tr>
<td>Peyote and Mescaline</td>
<td>Peyote is a spineless cactus which grows round fleshy tubercles which contain the active hallucinogen, mescaline. Mescaline intoxication is characterized by two distinct phases. Within an hour of ingestion, nausea, vomiting, diaphoreses, and mydriasis usually occur. This is followed by a psychoactive stage resembling LSD intoxication which lasts approximately 12 hours.</td>
</tr>
<tr>
<td>Morning Glory</td>
<td>Seeds of the Morning Glory contain compounds related to lysergic acid. When crushed and ingested, an LSD-like toxidrome typically occurs.</td>
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<tr>
<td>Jimsonweed; (aka. Thornapple)</td>
<td>Seeds of this wild plant called <em>Datura stramonium</em>, contain powerful anticholinergic alkaloids. These seeds may be chewed or smoked for its hallucinogenic properties. This plant can be found all over the US. It frequently grows on highway roadsides.</td>
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<tr>
<td>Nutmeg</td>
<td>Dried seed kernal of the fruit of a tall evergreen tree native to the South Pacific, Grenada, and Trinidad. The toxic dose is generally 3 whole nutmegs or 10-15 grams of dried spice. Intoxicated patients are generally miserable and often have a sense of impending doom. Symptoms may consist of nausea, epigastric pain, facial flushing, decreased salivation, miosis and hypothermia.</td>
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**Treatment of Hallucinogen Intoxication**

- Hallucinogen (usually LSD) intoxicated patients usually present to the ER because they are on a “bad trip”. Frightening thoughts overwhelm the user, with a loss of insight that this is a drug experience resulting in an acute panic reaction.

- Acute mania, schizophrenia, depression and permanent psychosis have been attributed to long-term LSD abuse.

- Treatment of acute intoxication is handled by reassurance, relaxation techniques in a quiet environment, and appropriate symptomatic treatment. Severe panic reactions or violent behavior may be treated with *diazepam* or midazolam (*Versed*). Phenothiazines may be considered for severe hallucinogenic reactions. Phenothiazines must be used with caution because of a small theoretical risk of lowering the seizure threshold or exacerbating flashback reactions. [*Haldol*: 0.1-0.2 mg/kg IM or IV over 1 minute. May repeat once after 20-30 minutes and hourly prn].

- The administration of an SSRI may severely aggravate the degree of psychosis in the LSD intoxicated patient, and must be avoided.

- Physostigmine (1 mg infused SLOWLY over 5-10 minutes; may repeat q 20-40 minutes prn) may be considered for serious hallucinations and psychosis attributed to *Jimsonweed* intoxication. The patient must be on a heart monitor and atropine must be at the bedside during administration.

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**CANNABIS**

1/11/04
Since the 1960s, marijuana has easily retained its title as the most predominate illicit drug used in the United States. In a recent national high school survey, 40% of seniors reported lifetime, 31% reported annual use, and 3.6% reported daily use. Annual marijuana use by 20 year-olds is estimated to be 30%, and in 30 year-olds, 20%.

Pharmacology: Effects attributed to metabolite $^9$-tetrahydrocannabinol (THC). Mechanisms of action are not well understood.

ACUTE CLINICAL EFFECTS

CNS: Euphoria, relaxation, altered time/space perception, impaired short-term memory, problems with frequency of speech and organization of thought, impaired ability to perform complex tasks or complex motor functions.

CARDIOVASCULAR: Tachycardia due to a stimulated autonomic nervous system.

RESPIRATORY: Similar to tobacco smoking, deep inhalation and retention of smoke may result in coughing and local irritation.

CHRONIC CLINICAL EFFECTS

The long-term effects of chronic marijuana use remains an area of intense research. Chronic pulmonary effects are similar to that produced by chronic tobacco use. Abnormalities in sperm count, motility, and structural characteristics have been reported in male marijuana users but no definitive evidence shows that marijuana alters sexual function in either males or females to an extent that reproduction is impaired.

GAMMA-HYDROXYBUTYRATE

<table>
<thead>
<tr>
<th>Gamma-hydroxybutyrate</th>
<th>“Scoop”</th>
<th>“Liquid X”</th>
<th>“Liquid “Ecstasy”</th>
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<tbody>
<tr>
<td>GHB</td>
<td>Somatomax PM</td>
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<tr>
<td>“White Rhino”</td>
<td>“Liquid X”</td>
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<table>
<thead>
<tr>
<th>Gamma-butyrolactone</th>
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<tbody>
<tr>
<td>GBL</td>
<td>Reivvarant</td>
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<tr>
<td>4-butyrolactone</td>
<td>Renewtrient</td>
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<tr>
<td>Blue Nitro</td>
<td>Gamma G</td>
<td></td>
<td></td>
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<tr>
<td>Remforce</td>
<td>GH Revitalizer</td>
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HISTORY

- GHB was originally developed 30 years ago for use as an anesthetic but failed to find a role in medical practice because of concerns regarding potential seizure activity during research trials.

- GHB was later reintroduced in the 1980s in health-food stores as a food supplement for body builders. In 1990, GHB was banned by the FDA from OTC sale and now remains an investigational agent used experimentally for the treatment of narcolepsy.

- GHB prominence is growing in the underground market for recreational drugs of abuse. It is primarily sought for its reported ability to act as a growth hormone stimulant, diet aid, hypnotic, and euphoriant. It is also been implicated in a number of ‘date rape’ cases.

- Extensive information on GHB including a recipe for manufacturing GHB can be found on the internet. (www.erowid.com/entheogens/ghb/ghb.shtml or www.frsa.com/bbmsgs/messages/5881.html)

- GBL is converted to GHB in the body. The FDA recently issued a warning regarding the hazards of GBL and requested that companies that distribute GBL containing products issue a recall. Products containing GBL are marketed under various brand names (see above GBL table) and sold primarily in health food stores and fitness
centers. These products are also sold extensively over the internet. They are promoted with claims to build muscle, improve physical performance, enhance sexual performance, reduce stress, and induce sleep.

- GHB is now on a bifurcated controlled substance schedule. In the ‘illicit’ form, GHB is a schedule I substance. ‘Medical’ GHB when used for treatment of such disorders as narcolepsy, is a schedule III substance.
- GHB is currently under investigation for use in the treatment of refractory narcolepsy. If taken 2 times every night it appears to be very effective in restoring normal sleep patterns, especially REM sleep efficiency. Its mechanism of action is not well defined, but its efficacy appears to be superior to traditional narcolepsy treatment modalities.

PHARMACOLOGY
GHB is an endogenous constituent of mammalian origin that is present in virtually all tissues. Its exact site and mechanism of action producing the clinical effects is not well understood. GHB is not, however, a nutritional requirement. Its metabolic role is uncertain but it is thought to act as a central neurotransmitter or neuromodulator. It is both a metabolite and a precursor to the neurotransmitter GABA, the primary inhibitory neurotransmitter of the CNS. GHB is also chemically similar to glutamic acid.
- Temporarily inhibits dopamine release in the CNS. This may cause increased dopamine storage, and later increased release when the GHB is removed.
- Stimulants pituitary release of growth hormone
- Increases in prolactin serum concentrations reported with use of GHB.
- May stimulate the release of endogenous opioids.
- May act as a GABA agonist, but further research is required to verify such activity.
- May stimulate the release of acetylcholine in the CNS.
- Sleep inducing properties appear to be due to the conversion of the metabolite gamma hydroxybutyrolactone to its free acid.

KINETICS
Absorption and Distribution: GHB is rapidly absorbed following ingestion. It has low protein binding and readily crosses the blood-brain-barrier and placental barriers.

Peak effect: 2-15 minutes with IV administration; 15-60 minutes with oral administration
Duration: Effects last from 1.5 to 3 hours but may exceed 8 hours.
Metabolism: Research on metabolism is limited, but GHB is believed to be converted to succinic semialdehyde and gamma-aminobutyric acid (GABA). Ultimately, it is converted to CO2 and water and eliminated primarily through expired breath as CO2. <2-5% of the parent GHB is eliminated in the urine. Its elimination half-life is approximately 30 minutes.

REPORTED CLINICAL EFFECTS

<table>
<thead>
<tr>
<th>Effect</th>
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<tbody>
<tr>
<td>headache</td>
</tr>
<tr>
<td>dizziness</td>
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<tr>
<td>lethargy; coma</td>
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<tr>
<td>amnesia</td>
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<tr>
<td>tremors</td>
</tr>
<tr>
<td>euphoria</td>
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<tr>
<td>delirium</td>
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<tr>
<td>hypotonia</td>
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<tr>
<td>hypotension</td>
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<tr>
<td>respiratory depression</td>
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<tr>
<td>diaphoresis</td>
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<tr>
<td>hypothermia</td>
</tr>
<tr>
<td>hallucinations</td>
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<tr>
<td>bradycardia</td>
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<tr>
<td>seizure-like activity**</td>
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</tbody>
</table>

**Seizure-like activity:** proposed ketamine-like movements of the face and extremities that have been postulated by some clinicians to be misinterpretations of seizure activity. It is still unknown whether GHB intoxication produces seizure activity. Animal studies of GHB toxicity found that the lethality was attributed to respiratory depression.

DOsing/FORMULATIONS
- Exhibits a dose related effect although the response appears to vary between individuals.
- Toxicity is obviously dependent on the purity of the GHB sample.
• GHB is distributed as the sodium salt form as a powder that readily dissolves in a liquid or may formulated in a tablet or capsule form.

<table>
<thead>
<tr>
<th>DOSE</th>
<th>CLINICAL EFFECT</th>
</tr>
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<tbody>
<tr>
<td>20 mg/kg</td>
<td>REM and non-REM sleep; amnesia</td>
</tr>
<tr>
<td>20-30 mg/kg</td>
<td>Treatment of narcolepsy</td>
</tr>
<tr>
<td>50 mg/kg</td>
<td>anesthesia</td>
</tr>
<tr>
<td>&gt;50 mg/kg</td>
<td>decreased cardiac output, respiratory depression, seizure-like activity and coma</td>
</tr>
</tbody>
</table>

MANAGEMENT
- Involves primarily supportive care. Prognosis is generally quite good.
- ABCs; oxygen, IV access, intubation, temperature control
- Rule-out polysubstance intoxication
- GI decontamination with activated charcoal

**Naloxone:** Should be used in cases when other drugs (i.e. opiates) are suspected. Naloxone has been shown to be beneficial in reversing GHB toxicity in animal studies but has shown variable effects in several human cases.

**Neostigmine:** Human trials of GHB induced anesthesia demonstrated a safe and rapid reversal of GHB intoxication after physostigmine or neostigmine administration. The documentation of efficacy and safety of these potent cholinergic agents during acute GHB poisoning is lacking. Until more recent trials are performed, routine use of physostigmine or neostigmine is strongly discouraged.

**Flumazenil:** Has been proposed to antagonize GHB growth hormone secretory effects in humans. Flumazenil has shown no beneficial clinical effects during GHB intoxication, therefore its routine use should not be advocated or recommended.

**Antiepileptic agents:** Various agents have been tried in human case reports with variable results. The role of anticonvulsants in managing suspected GHB-induced seizures is unknown.

LABORATORY ANALYSIS
• 4-hydroxybutyrate can be extracted plasma as 4-butyrolactone and analyzed using gas chromatography. There are currently no standard or universally accepted assays for GHB analysis.
• There are currently no national reference laboratories that will conduct routine testing for GHB in biological samples, therefore, a definitive diagnosis of GHB poisoning is difficult to obtain unless a clear history of exposure is obtained.

CONCLUSIONS
• There is relatively little known about GHB which at one time was considered “nontoxic”.
• There is no antidote to immediately reverse its effects.
• GHB must now be included in the differential diagnosis of patients who present with unexplained seizure-like activity and or coma, especially in individuals who are body builders, dieters, or health fanatics.
  • A word of warning for those who continue to use GHB…**caveat emptor, (buyer beware)**

**INHALANT ABUSE**
• “Huffing”, “Bagging”, “Whip-its”.
• Vast majority of inhalant abusers are between the ages of 10-17 years, with reported abuse highest among eighth graders.
• It is estimated that 1 in 5 adolescents will have abused volatile substances at least once in their life.
• Volatile substance abuse among adolescents is rising to a much greater degree than any other form of substance abuse.
• As many or more kids die from inhalant abuse as from all other drugs combined with the exception of possibly ethanol.

<table>
<thead>
<tr>
<th>OVER-THE COUNTER PRODUCTS</th>
<th>CHEMICAL AGENTS</th>
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<tbody>
<tr>
<td>Lighter Fluid</td>
<td>Butane, propane</td>
</tr>
<tr>
<td>Aerosol Air Fresheners, liquid aroma products</td>
<td>Butane</td>
</tr>
<tr>
<td>Marker pen Ink</td>
<td>Toluene, xylene</td>
</tr>
<tr>
<td>Adhesive Cements and model glues</td>
<td>Toluene, trichloroethane</td>
</tr>
<tr>
<td>Spray Paints</td>
<td>Methyl ketones, toluene, xylene</td>
</tr>
<tr>
<td>Lacquer thinners</td>
<td>Xylene, toluene, methyl ethyl ketones</td>
</tr>
<tr>
<td>Paint and varnish removers</td>
<td>Methylene chloride</td>
</tr>
<tr>
<td>Typewriter correction fluid</td>
<td>1,1,1 trichloroethane or trichloroethylene</td>
</tr>
<tr>
<td>Whipped Cream Canisters</td>
<td>Nitrous Oxide</td>
</tr>
<tr>
<td>VCR Head Cleaning Fluid</td>
<td>Butyl Nitrite (“rush”, “locker room”)</td>
</tr>
</tbody>
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**ACUTE INHALANT INTOXICATION**
- Mood altering effects consist of euphoria, slurred speech, dizziness, and excitability, along with hallucinations.
- Clinical findings of acute inhalant abuse also include ataxia, diplopia, nystagmus, flushing, and varying degrees of CNS depression.
- “SUDDEN SNIFFING DEATH” (SSD) is a phrase used to describe the unpredictable occurrence of an acute fatal cardiopulmonary arrest in the inhalant abuser. SSD likely occurs as a combination of hypoxia, respiratory depression, vagal stimulation and/or frank cardiac arrhythmia. SSD can occur in anyone, of any age, and at any time, even the first time inhalants are abused. The mechanism of toxicity is unclear, but the leading theory maintains that volatile hydrocarbons may sensitize the myocardium to catecholamines resulting in an arrhythmogenic effect.
- Volatile hydrocarbons are rapidly cleared from the systemic vasculature making routine blood or plasma assays of little value. Volatile solvents are lipophilic and may remain in cell membranes for extended periods of time resulting on a protracted course of intoxication.

**CHRONIC INHALANT INTOXICATION**
- Cardiomyopathy, emphysema, reactive airway disease, distal type I renal tubular acidosis, reversible centrilobular hepatic necrosis, encephalopathy, cognitive impairment, cerebellar damage.
- Peripheral neuropathy caused by chronic glue sniffing may be confused with Guillain-Barre syndrome; axonal swelling found on sural nerve biopsy is characteristic of the former but not typically seen with the latter.

**DIAGNOSIS**
Without a comprehensive and forthcoming abuse history it is very difficult to identify inhalant abuse. There are no readily available laboratory tests that can be conducted to identify an exposure to volatile hydrocarbons. Inhalant abuse must be ruled out in the otherwise healthy young adolescent who presents with CNS depression, profound behavioral changes, sudden unexplained cardiopulmonary arrest, other neurological abnormalities, liver abnormalities, or kidney impairment. Typically, the heavy user may present with a strong solvent smell emanating from the hair, clothing or breath. A peculiar rash may also be found around the nose, mouth, face, and neck of an inhalant abuser coining the term “Glue Sniffer’s Rash”. Laboratory testing is going to be guided by the type of substance abused.

**SPECIFIC COMPOUNDS**
1. **Toluene**: A favorite of inhalant abusers because of the intense euphoric rush achieved with inhalation. Some users even go to the extent of abusing specific colors of spray paint (usually gold or silver) because they generally have a higher toluene content. Model glue sniffing is also a popular form of toluene abuse. Heavy
Toluene abuse can result in sudden fatal arrhythmias and permanent CNS impairment, including tremors, ataxia, cerebellar and cerebral atrophy, and cognitive and neurobehavioral abnormalities. Myopathy, hypokalemia, renal tubular acidosis, and renal impairment are also common findings. Following recent heavy abuse, the abuser may also present with the characteristic finding of hyperchloremic acidosis. For this reason, toluene is included in the AT MUD PILES mnemonic for metabolic acidosis. Xylene possesses a similar toxicity profile as toluene.

**Diagnosis:** Toluene abuse or the confirmation of abstinence may be aided by a urinary analysis for metabolites of toluene (hippuric acid). Blood toluene levels may also be requested. These laboratories test are not usually readily available and may take several days to weeks to retrieve results. Laboratory work-up should include renal function tests, CPK (elevated with toluene abuse), a complete electrolyte panel and possibly an ABG.

2. **Butane:** Commonly used propellant in numerous aerosol products such as air fresheners. It can also be purchased in pure form with butane lighter refill canisters. Numerous reports of SSD have been reported of adolescents “huffing” aerosol air fresheners or butane lighter refill canisters.

3. **Nitrous Oxide (“Laughing gas”):** Acute toxicity is generally associated with asphyxia. Chronic abuse leads to the selective inhibition of vitamin B12 resulting in a number of hematological and neurological abnormalities associated with Vitamin B12 deficiency. These patients will, however, have normal vitamin B12 levels.

4. **Butyl nitrite:** Abused as a euphoriant and aphrodisiac. Heavy use may produce methemoglobinuria.

   Methemoglobin is an oxidized form of hemoglobin which is incapable of carrying oxygen, inducing a functional anemia. Methemoglobinemia also shifts the oxygen dissociation curve to the left, thereby rendering normal hemoglobin less able to release oxygen to the tissue resulting in cellular hypoxia. When methemoglobin exceeds 20%, significant toxicity ensues with headache, dizziness, and nausea, progressing to dyspnea, confusion, seizures, and coma. Skin discoloration (“chocolate cyanosis”) is characteristically found on the nail beds, lips, and ears. Methemoglobinemia should be suspected in those patients who present with the above symptoms, do not respond to oxygen therapy, and display a normal PO2. These patients may have a “chocolate-brown” color to their blood which can be identified by placing a drop of their blood on white filter paper and comparing it to a normal blood drop. Ideally, a methemoglobin level will confirm the diagnosis, but most hospitals are incapable of measuring methemoglobin levels.

5. **Trichloroethylene and trichloroethane:** Chlorinated hydrocarbons found in typewriter correction fluid and solvent cleaners. Abuse has been associated with fatal arrhythmia, peripheral neuropathy, hepatic failure, renal failure, and CHF.

6. **Methylene Chloride:** Found in paint and varnish strippers. Metabolized to carbon monoxide in the body. May produce renal damage as well.

**TREATMENT**

- Symptomatic and supportive care.
- Oxygen is required for suspected carbon monoxide poisoning following a toxic methylene chloride exposure.
- Controversy surrounds the use of exogenous catecholamines to treat volatile hydrocarbon-induced arrhythmias. The concern stems from the mechanism of toxicity where volatile hydrocarbon inhalants may sensititize the myocardium to the arrhythmogenic effects of catecholamine.

**Methemoglobinemia:** *Methylene Blue* 1-2 mg/kg IV over 5 minutes. May be repeated in 30-60 minutes.

**REFERENCES**

**Opioids**


**Hallucinogens**

**GHB**

**Inhalant Abuse**

**Substance Withdrawal**