Over-the-Counter analgesics

ACETAMINOPHEN

- Acetaminophen is contained in more than 100 over-the-counter drug preparations and is routinely reported as the most common pharmaceutical agent involved in overdose.
- Hepatic failure due to acetaminophen overdose is the most common cause of liver failure requiring transplantation in the United Kingdom and in the United States.
- Acetaminophen toxicity is an example of saturation of deactivation pathways.
Metabolism of acetaminophen showing activation and detoxication pathways

- O-Glucuronide
- HNCCCH<sub>3</sub>
- Cell Death
- Covalent binding to SH groups of protein
- Glucuronyl transferase
- UDPGA
- Glutathione-S-transferase
- GSH
- Sulfotransferase
- PAPS
- HNCOCH<sub>3</sub>
How does acetaminophen cause toxicity?

• Under normal metabolic conditions and recommended doses, 90-93% of acetaminophen is conjugated in the liver to glucoronide and sulphates conjugates, which are eliminated in the urine.
• About 2% of acetaminophen is eliminated unchanged by the kidneys.
• 5% of acetaminophen is metabolized oxidatively by the cytochrome P450 mixed-function oxidase system in the liver. This route of metabolism creates a reactive intermediate: quinoneimine \{N-acetyl-para-benzoquinoneimine (NAPQI)\}.
NAPQI

- NAPQI is rapidly bound to glutathione and detoxified.
- When glutathione levels fall to less than 30% of normal, NAPQI is free to bind to hepatocyte membranes and cause cell death and liver necrosis.

Acetaminophen overdose

- If too much acetaminophen is around, the conjugation and sulfation metabolic routes are saturated.
- This means more of the parent acetaminophen compound is metabolized by the P450 system, which forms more of the toxic metabolite NAPQI.
Factors influencing toxicity

- Chronic alcoholics are at increased risk of developing severe hepatic diseases even at therapeutic doses.
- Other drugs which induce CYP2E1 enzymes include phenobarbital, isoniazid, and rifampin because they lower the cellular glutathione stores.
- Drugs such as sulfa and AZT (zidovudine) potentiate acetaminophen hepatotoxicity by competing for glucuronidation pathways resulting in increased CYP2E1-dependent metabolism of acetaminophen.
- Malnutrition may predispose to acetaminophen toxicity by a reduction in glutathione stores.
What dose of acetaminophen causes toxicity?

- The recommended therapeutic dose of acetaminophen over a 24-hour period is 4 gm in adults and 90 mg in children.

- A dose of 150 mg/kg or 7.5 gm in adults can cause toxicity (exceptions: patients who are taking anticonvulsants or rifampin, patients with history of chronic ethanol abuse, fasting, malnutrition, or HIV infection).
The time course of acetaminophen toxicity

- Phase 1: (up to about 24 hours), patient has anorexia, nausea; transaminases are rising.
- Phase 2: (24-72), right upper quadrant pain develops; transaminases are peaking; bilirubin and prothrombin time (PT) elevated.
- Phase 3: (72-96), hepatic necrosis is characterized by jaundice, coagulopathy, encephalopathy, acute renal failure, and death.
- Phase 4: (96hrs-14days), resolution of liver dysfunction and healing of the pathologic liver damage.
Diagnosis

- In patient with a history of acetaminophen overdose, a serum acetaminophen level should be measured between 4 and 24 hours after ingestion.
- The value obtained should be evaluated according to the Rumack-Matthew nomogram for determining the risk of hepatotoxicity and need for therapy.
- Rumack-Matthew nomogram is semi-logarithmic plot of plasma acetaminophen levels vs. time. Its based only on acute ingestion.
- Acetaminophen levels are measured ≥ 4hrs after ingestion and 4 hrs later; if either level is above the Rumack-Matthew line of toxicity, treatment is required.
How to estimate the risk of hepatotoxicity? (Rumack-matthew nomogram)

Rumack-Matthew nomogram.
The antidote is N-acetylcysteine (NAC) (mucomyst). It acts as a precursor to cysteine, and then to glutathione. By replenishing glutathione stores, it provides sulfhydryl donors to which NAPQI can bind and detoxify. It may also enhance sulfation of any remaining acetaminophen, result in reduction in the amount of NAPQI. NAC acts as a free radical scavenger, by enhancing oxygen uptake and utilization in peripheral tissues.

Acetaminophen hepatotoxicity antidote
NAC administration

- NAC should be administered anytime within 8 hours of ingestion, it is nearly 100% protective against hepatotoxicity.
- The NAC protocol (orally): 140 mg/kg loading dose, followed by 17 doses of 70 mg/kg administered every 4 hours for a total of 1330 mg/kg over 72 hours.
- Intravenous NAC protocols: (1)- 150 mg/kg of IV NAC over 15 minutes; this is followed by 50 mg/kg IV over 4 hours, followed by 100 mg/kg over 16 hours. (2)-140mg/kg IV over 1 hour followed by 12 doses of 70 mg/kg administered every 4 hours.
Special considerations for pregnant patient and children

• Acetaminophen has been shown to cross the placenta and do cause hepatotoxicity in a fetus which has functioning mixed-function oxidase liver enzymes.
• Pregnant patient should receive NAC for treatment with no delay.
• Children may fare better after ingestion of acetaminophen because of an enhanced capacity for sulfation in their livers.
• Using 2-hours acetaminophen levels to predict toxicity risk after the ingestion of liquid acetaminophen formulas.
Salicylates toxicity

• Background: salicylates possess anti-inflammatory, analgesic, and antipyretic properties.
• These agents are available as for ingestion as tablets, capsules, liquids, and in topical forms as creams and lotions.
• Packaging laws have decreased pediatric access to quantities of aspirin and pediatric use has declined because of aspirin’s association with Reye’s syndrome and increase acetaminophen utilization.
• Aspirin (salicylic acid) continues to be a significant source of poisoning for both intentional and unintentional overdose with about 18,000 poisonings a year in USA.
What products other than aspirin contain salicylates?

- More than 200 aspirin-containing products are available in USA.
- Aspirin is often combined with antihistamines, decongestants, and other cold and cough and arthritis preparations.
- Oil of wintergreen (4ml dose of oil wintergreen has caused death in children).
- Topical salicylic acid is used as keratolytic.
- Pepto-Bismol (bismuth subsalicylate) contains 8.8 mg/ml. The 240 ml dose commonly used for traveler’s diarrhea contains the equivalent of eight 325 mg tablets.
How much aspirin is too much?

- Acute ingestion of 150-200 mg/kg (one-half to one 325 mg tablet per kg) produce mild symptoms such as gastritis, bleeding and vomiting, whereas 300-400 mg/kg produce serious toxicity.
- On the other hand, chronic ingestion of 100 mg/kg/day for 2 days or more will produce symptoms of chronic toxicity (gastroenteritis symptoms may be absent, usually brought in because of changes in mentation).
How does salicylate cause acid-base disorders?

• The primary result of high serum concentrations of salicylic acid is interference with acid-base balance.
• The stability of serum pH (7.4) depends on the maintenance of a delicate ratio of bicarbonate ion to carbonic acid (HCO$_3^-$/$H_2CO_3$:20/1).
• As salicylic acid levels rise and pH decrease, the medullary respiratory center is stimulated resulting in hyperventilation.
• Initially a respiratory alkalosis develops secondary to direct stimulation of the respiratory centers. This may be the only consequence of mild salicylism.
Mechanism of Respiratory Alkalosis

- Normal bicarbonate equilibrium:
  \[ \text{H}_2\text{O} + \text{CO}_2 \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}^+ + \text{HCO}_3^- \]

- Effect of increased CO\(_2\) loss is to pull the equilibrium away from hydrogen ion (shifts to the left)
  (reduce the concentration of hydrogen ion = raise the pH)
  \[ \text{H}_2\text{O} + \text{CO}_2 \text{ (drops)} \leftrightarrow \text{H}_2\text{CO}_3 \text{ (drops)} \leftrightarrow \text{H}^+ + \text{HCO}_3^- \]

- Respiratory alkalosis with compensatory metabolic acidosis and dehydration defines the next stage in moderate to severe intoxication.
Biochemical abnormalities in salicylate overdose

SALICYLATE OVERDOSE

- Stimulation of respiratory center
  - Elevated breathing rate
    - Loss of carbon dioxide
      - Respiratory alkalosis

- Uncoupling of oxidative phosphorylation
  - Increase in glycolysis
    - Lactic acid accumulation
      - Metabolic acidosis

- Inhibition of TCA cycle enzymes
  - Accumulation of TCA polycarboxylic acids
      - Metabolic acidosis
# Pathology and mechanism of salicylates toxicity

<table>
<thead>
<tr>
<th>Mechanism of Toxicity</th>
<th>Pathological Consequence</th>
<th>Metabolic Compensation</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated ASA serum concentration (acidic</td>
<td>Decreases serum pH</td>
<td>Contributes to metabolic acidosis; alters platelet function (hypoprothrombinemia)</td>
<td>Increases bleeding time</td>
</tr>
<tr>
<td>substance)</td>
<td></td>
<td>Decreases plasma PCO₂ with respiratory alkalosis</td>
<td></td>
</tr>
<tr>
<td>Stimulation of medullary respiratory center</td>
<td>Hyperventilation</td>
<td></td>
<td>Tachypnea, pulmonary edema, tachycardia,</td>
</tr>
<tr>
<td>Renal compensation for respiratory alkalosis</td>
<td>Kidneys excrete more bicarbonate</td>
<td>Contributes to compensatory metabolic acidosis; CNS toxicity</td>
<td>dehydration</td>
</tr>
<tr>
<td>Inhibition of Kreb’s cycle enzymes</td>
<td>Accumulation of organic acids</td>
<td>Contributes to metabolic acidosis and lactic acidosis</td>
<td>Irritability, restlessness, tinnitus,</td>
</tr>
<tr>
<td>Oxidative uncoupling of electron transport</td>
<td>Prevents combination of phosphate with ADP</td>
<td>Decreases formation of ATP, enhanced glycolysis, lactic acid, pyruvic acid; contributes to metabolic acidosis</td>
<td>dehydration, seizures, coma</td>
</tr>
<tr>
<td>chain</td>
<td></td>
<td></td>
<td>Gastric irritation, nausea, vomiting</td>
</tr>
<tr>
<td></td>
<td>Increases peripheral demand for glucose</td>
<td>Stimulates lipid metabolism, releases fatty acids, contributes to metabolic acidosis</td>
<td>Hyperthermia, tachycardia, dehydration,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cardiovascular collapse, hypoglycemia</td>
</tr>
</tbody>
</table>
What is a toxic level of salicylates?

- Classification of acute salicylates poisoning (3-6 hours post-ingestion) according to serum salicylate level:
  - Moderate: 50 mg/dl
  - Severe: 75 mg/dl
  - Potentially lethal: 100 mg/dl (correlates with seizures)

- Alan Done nomogram correlates salicylates levels at different times after ingestion of single acute overdose to determine the severity of the poisoning.

- Because of the delay in absorption, the nomogram is not used to determine treatment, unlike the acetaminophen monogram.

- Treatment decisions must be based on clinical symptoms and laboratory test abnormalities rather than serum levels alone.
The difference between salicylates acute and chronic poisoning

- Acute poisoning produces vomiting, GI irritation and bleeding, hyperpnoea, tinnitus and lethargy. Respiratory alkalosis and metabolic acidosis follow. Severe poisoning can result in restlessness, irritability, seizures, coma, hyperthermia, hypoglycemia and pulmonary edema,

- Chronic poisoning is more likely to produce nonspecific symptoms such as lethargy, confusion, hallucination, metabolic acidosis and dehydration. Death occur from pulmonary edema or cerebral edema, is more common in patients with chronic poisoning than with acute poisoning and occurs at lower salicylates level.
Morbidity/mortality

- A 16% morbidity rate and a 1% mortality rate are associated with patients presenting with an acute overdose. The incidence of morbidity and mortality of a patient with chronic intoxication is 30% and 25% respectively.
- The following 4 categories are helpful for assessing the potential severity and morbidity of acute intoxication:
  1. Less than 150 mg/kg  no toxicity to mild toxicity
  2. From 150-300 mg/kg  mild to moderate toxicity
  3. From 300-500 mg/kg  serious toxicity
  4. Greater than 500mg/kg  potentially lethal toxicity.
What is the time course of salicylate toxicity?

• Symptoms can begin within 1-2 hours after an acute ingestion or may be delayed for more than 4-6 hours. Absorption usually occurs over a few hours but can be delayed after the ingestion of sustained-release or enteric-coated preparations.

• In addition, salicylate can form concretions in the stomach; these concretions can continue to release drug slowly, producing rising serum levels for up to 12 hours.

• Severity of symptoms sometimes does not peak until 12-24 hours. However, if there are no symptoms within 6 hours, it is unlikely that the patient will experience severe toxicity, unless a sustained-release preparation was ingested.
Clinical symptoms

- Pulmonary: hyperventilation (common), pulmonary edema, respiratory arrest, apnea.
- Auditory: ototoxicity, tinnitus (common when serum salicylates exceed 30 mg/dl), deafness.
- Cardiovascular: tachycardia, dysrhythmias, ECG abnormalities due to hypokalemia.
- Neurologic: CNS depression, seizures, encephalopathy, cerebral edema (associate with severe cases).
- GIT: nausea and vomiting (common), GI hemorrhage. Pancreatitis, hepatitis.
- Hematologic: prolongation of prothrombin and bleeding times and decrease platelets adhesiveness.
- Electrolytes: dehydration, hypokalemia, hypocalcaemia, acidemia.
- Body temperature increased (hyperthermia).
As an antipyretic, aspirin decrease body temperature. How can it increase temperature in an overdose?

- Salicylates cause an uncoupling of oxidative phosphorylation (that allow oxidation in mitochondria to proceed without the usual concomitant phosphorylation to produce ATP).
- The inhibition of ATP-dependent reactions result in:
  - Increased oxygen consumption, glucose use, and heat production.
  - Increased carbon dioxide production
  - Accelerated activity of the glycolytic and lipolytic pathways. Depletion of hepatic glycogen.
- This results in fever, tachypnea, tachycardia, and hypoglycemia.
Laboratory tests

- Serum salicylates level.
- Arterial blood gases.
- Electrolytes (especially potassium).
- Complete blood count (BCB).
- Glucose.
- Blood urea nitrogen (BUN).
- Creatinine.
- Liver function tests.
- Prothrombin time.
- Urine pH.
- X-rays.
What is the treatment for salicylates poisoning?

• There is no antidote for salicylates poisoning.
• Always begin with supportive care. Maintain the airway and assist ventilation if necessary. Administer supplemental oxygen. Obtain serial arterial blood gases and chest x-rays to observe for pulmonary edema (more common with chronic or severe intoxication).
• Treat coma, seizures, pulmonary edema, and hyperthermia if they occur.
• Treat metabolic acidosis with intravenous sodium bicarbonate. Do not allow the serum pH to fall below 7.4.
• Replace fluid and electrolyte deficits caused by vomiting and hyperventilation with intravenous crystalloid solutions. Sodium bicarbonate is frequently given both to prevent acidemia and to promote salicylates elimination by the kidneys.

• Give vitamin K as needed for coagulopathy.

• Except in cases where there are severe symptoms that need to be treated first, activated charcoal is usually the first intervention.
Decontamination is not necessary for patients with chronic intoxication.

1. Prehospital: Administer activated charcoal if available promptly.
   - If activated charcoal is given promptly, lavage is not necessary after small ingestions (i.e., >200-300 mg/kg).

2. Hospital: Administer activated charcoal orally or by gastric tube. Gastric lavage is not necessary after small ingestions (i.e., <200-300 mg/kg) if activated charcoal is given promptly.

   I. Exposure
   - Children at home: If it can be given within 30 minutes of ingestion, ipecac-induced emesis may be useful for initial treatment of ipecac-induced emesis.
   - If ipecac is not available, activated charcoal, if available, should be given.

   1. Hospital: Administer activated charcoal, if available.
Enhanced elimination

• Urinary alkalization using sodium bicarbonate.
• Repeated-doses of activated charcoal therapy effectively reduces the serum salicylates half-life.
• Hemodialysis is very effective in rapidly removing salicylates and correcting acid-base and fluid abnormalities.
• Hemoperfusion is also very effective but does not correct acid-base or fluid disturbances.
Is death from salicylates poisoning possible?

- Absolutely! Death may be secondary to cardiovascular collapse, CNS overstimulation that causes seizures and hyperthermia, or pulmonary edema. Poison centers report about 35 deaths per year across the USA.
CNS DEPRESSANTS

What are Sedatives-Hypnotics

• The terms sedative and hypnotics are equivalent to central nervous system (CNS) depressants.
• A sedative is a substance that diminishes environmental awareness and physical activity.
• A hypnotic is an agent that induces sleep.
• Tranquilizers, or relievers of anxiety.
• All of these agents depress the CNS and produce progressive, dose-dependent alterations in behavior which are described as being depressant in action.
The stages of behavioral sedation

NORMAL

MENTAL RELAXATION

LOSS OF INHIBITIONS

SEDATION

SLEEP

ANESTHESIA

DEATH

INCREASING AMOUNTS OF DRUG
Principles of CNS depressants

- The effects of CNS depressants are additive (because the mechanisms of action of these compounds are similar).
- Depressants effects of these drugs are often supra-additive, i.e., the observed effect is greater than predicted.
- CNS depressants are antagonized by stimulants.
- General depressants depress all neurons within the brain.
- They induce physical dependence and produce withdrawal symptoms after chronic use.
- CNS depressants produce tolerance.
- Cross tolerance occurs.
History of CNS depressants

• The earliest sedatives were plant products.
• Bromides were introduced into medicine in 1857 and used in huge quantities as anticonvulsants as well as sedatives.
• Barbiturates were found to have medical properties in the early 20th century when barbital was marketed as hypnotic in 1903.
• Phenobarbital was introduced in medicine in 1912.
• Barbiturates and bromides were almost the only sedative agents available until the 1950s.
• Benzodiazepines were synthesized in 1933, and they have been used mainly as anti-anxiety agents since 1960.
Barbiturates

- Barbiturates were synthesized in the nineteenth century. In 1864 Adolph von Baeyer prepared barbituric acid from malonic acid and urea.
- Barbiturates are reversible general depressants of nerve and muscle tissues.
- Because of their potential toxicity, barbiturates have been largely supplanted by benzodiazepines as the most frequently prescribed sedative-hypnotics.
- Barbiturates continue to be used therapeutically for seizure control and general anesthesia, as well as for sedative-hypnotic effects.
pharmacokinetics

• The action duration of barbiturates is dependent in three processes: redistribution, metabolism, and excretion.

• Ultrashort-acting barbiturates are highly lipid soluble and rapidly penetrate the brain to induce anesthesia (IV), then are quickly redistributed to other tissues.

• Long-acting barbiturates are more water soluble and reach the CNS more slowly. They distributed more evenly and have long elimination half-lives, making them useful for once-daily treatment of epilepsy.
What are the different classes of barbiturates?

Barbiturates are usually grouped according to their pharmacokinetics

<table>
<thead>
<tr>
<th>GROUP</th>
<th>ONSET</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-short acting</td>
<td>Immediate after intravenous dose</td>
<td>Minutes</td>
</tr>
<tr>
<td>Short-acting</td>
<td>10–15 minutes after oral dose</td>
<td>6–8 hours</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>45–60 minutes</td>
<td>10–12 hours</td>
</tr>
<tr>
<td>Long-acting</td>
<td>1 hour</td>
<td>10–12 hours</td>
</tr>
</tbody>
</table>
# Common barbiturates

<table>
<thead>
<tr>
<th>Drug</th>
<th>Normal Terminal Elimination Half-Life (h)</th>
<th>Usual Duration of Effect (h)</th>
<th>Usual Hypnotic Dose (Adult) (mg)</th>
<th>Toxic Level (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrashort-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methohexital</td>
<td>3–5</td>
<td>&lt; 0.5</td>
<td>50–120</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Thiopental</td>
<td>8–10</td>
<td>&lt; 0.5</td>
<td>50–75</td>
<td>&gt;5</td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>15–50</td>
<td>&gt; 3–4</td>
<td>50–200</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Secobarbital</td>
<td>15–40</td>
<td>&gt; 3–4</td>
<td>100–200</td>
<td>&gt;10</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amobarbital</td>
<td>10–40</td>
<td>&gt; 4–6</td>
<td>65–200</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Aprobarbital</td>
<td>14–34</td>
<td>&gt; 4–6</td>
<td>40–160</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Butabarbital</td>
<td>35–50</td>
<td>&gt; 4–6</td>
<td>100–200</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Butalbital</td>
<td>35</td>
<td></td>
<td>100–200</td>
<td>&gt;7</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mephobarbital</td>
<td>10–70</td>
<td>&gt; 6–12</td>
<td>50–100</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>80–120</td>
<td>&gt; 6–12</td>
<td>100–320</td>
<td>&gt;30</td>
</tr>
</tbody>
</table>
How barbiturates work?

• All barbiturates caused generalized depression of neuronal activity in the brain.
• Barbiturates bind to molecular components of the GABA receptor present in the neural membranes in the CNS. This receptor, which functions as a chloride ion channel, is activated by the inhibitory neurotransmitter GABA.
• Barbiturates increase chloride entry by prolong the opening of the chloride channels. The larger number of open chloride channels the less excitable the membrane of the neurons.
• At high concentrations, the barbiturates may also be GABA-mimetic, directly activating chloride channels.
• Barbiturates also depress the actions of excitatory neurotransmitters such as glutamic acid.
• Barbiturates stimulates the release of GABA at sensitive synapses.

• Two major consequences account for the toxic manifestations:

1. Barbiturates decrease postsynaptic depolarization by acetylcholine, with ensuing postsynaptic block, resulting in smooth, skeletal, and cardiac muscle depression.

2. At higher doses, barbiturates depress medullary respiratory centers, resulting in inhibition of respiration.

• Hypotension that occurs with large doses is caused by depression of central sympathetic tone as well as by direct depression of cardiac contractility.
Toxic dose

- Barbiturates have long and well known history as a poisonous substances.
- In Europe from 1950 to 1970 they were a more common vehicle for suicide than all other methods combined.
- Barbiturates toxic dose varies widely and depends on the drug, route and rate of administration and individual tolerance.
- 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 is 2-3 g, compared with 6-10 g for Phenobarbital.
## Barbiturate Class vs. Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Therapeutic Concentration (mcg/dL)</th>
<th>Toxic Concentration (mcg/dL)</th>
<th>Lethal Concentration (mcg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
<td>10–100</td>
<td>700–1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>10–500</td>
<td>1000–3000</td>
<td>&gt;3000</td>
</tr>
<tr>
<td>Long-acting</td>
<td>1000–4000</td>
<td>4000–8000</td>
<td>&gt;8000</td>
</tr>
</tbody>
</table>
Signs and symptoms of acute toxicity

- They are related directly to CNS and CVS depression.
- The adverse effects of barbiturates are almost identical to those caused by alcohol.
- Mild to moderate intoxication: drowsiness, impaired intellectual and motor performance and judgment, lethargy, slurred speech, nystagmus, and ataxia.
- With higher doses: blood pressure and heart rate decline (hypotension), coma, and respiratory arrest commonly occur.
- Hypothermia is common in patients with deep coma. It results from depression of the thermoregulatory center in the brain.
- In severe overdose, respiratory and cardiac function are paralyzed and death results.
Clinical management of acute overdose

- Treatment of barbiturates overdose is largely supportive. There is no specific antidote.
- Emergency and supportive measures: maintaining adequate ventilation and supporting vital functions. Oxygen support, forced diuresis,
- Decontamination: activated charcoal, gastric lavage.
- Enhanced elimination by: alkalinization (only for phenobarbital), repeated dose of activated charcoal, hemoperfusion or hemodialysis.
- Incorporation of CNS stimulants in the treatment protocol is not recommended, since mortality rates from pharmacological antagonists are as high as 40%.
## Treatment essentials

### Basic Supportive Care

**Coma ± respiratory depression**
- Ensure adequate oxygenation, ventilation, and airway protection

**Hypotension**
- Fluid challenge with intravenous crystalloid (isotonic)
- Intravenous vasopressors as required:
  - Dopamine, 5–20 μg/kg/min
  - Epinephrine, 1 μg/min (titrate to effect)

**Hypothermia: body temperature >32°C**
- Prevent further heat loss:
  - Insulation (e.g., blankets)
  - Warm intravenous fluids
  - Heated humidified oxygen if intubated

**Hypothermia: body temperature <32°C**
- Consider aggressive active core rewarming techniques
- Consider cardiopulmonary bypass in cardiac arrest
- Aggressive management of sepsis
- Adequate antibiotic coverage
- Local wound care to prevent secondary infection

### Decontamination

**Activated charcoal**
- Adult, 50–100 g
- Pediatric, 1 g/kg
- Consider if massive ingestion

### Elimination

**Repeated-dose charcoal**
- Reduces elimination half-life of phenobarbital (no evidence to show that it improves outcome)
- 15–20 g (0.25 g/kg) q4–6 hr
- See text
- May be indicated for intractable hypotension
- Most effective for long-acting barbiturates

**Alkalization of urine**

**Hemoperfusion**
BENZODIAZEPINES

- Barbiturate deaths were very commonplace in the 1950s and 1960s.
- An intense search was ongoing within the pharmaceutical industry to find a safer alternative.
- Chlordiazepoxide (Librium) was the first of the benzodiazepines (1965) to be marketed as a sedative and an anxiolytic. Diazepam (Valium) followed soon after chlordiazepoxide and became even more popular.
- One hundred million prescriptions were written each year for benzodiazepines during the 1970s in the USA.
- As the danger of abuse became more clear, only 70 million prescriptions were written each year by the mid-1980s.
- By 1999, 28 different benzodiazepines were available worldwide, 13 of which were available by prescription in the USA. Most of these are taken to relieve anxiety.
Pharmacokinetics

• Benzodiazepines are extensively absorbed when taken orally and achieve peak blood concentrations in about 1 hour.

• Benzodiazepines become highly protein binding after absorption.

• Many of them are metabolized and excreted into bile from which they may undergo reabsorption back into blood.

• Most of them also are highly fat soluble.

• These three factors (protein binding, biliary recirculation, and fat storage) are major reasons why benzodiazepines often have very long half-lives.
# Categories of benzodiazepines

Benzodiazepines, like barbiturates, have been subclassified on the basis of duration of action

<table>
<thead>
<tr>
<th>Class</th>
<th>Half-life</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short acting</td>
<td>1–8 hours</td>
<td>Triazolam, Midazolam</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Approx. 1 day</td>
<td>Lorazepam, Oxazepam</td>
</tr>
<tr>
<td>Long acting</td>
<td>Up to several weeks</td>
<td>Chlordiazepoxide, Diazepam, Flurazepam</td>
</tr>
</tbody>
</table>
## Properties of benzodiazepines

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Proprietary Name</th>
<th>Classification</th>
<th>Sedative/Hypnotic Total Daily Dosage (mg)</th>
<th>Toxic Concentration</th>
<th>t₁/₂ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Xanax</td>
<td>Anxiolytic</td>
<td>0.25–1.5/0.5–1.0</td>
<td>0.4 µg/dl</td>
<td>12–19</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Librium</td>
<td>Anxiolytic</td>
<td>5–100/25–50</td>
<td>3.5–10 mg/l</td>
<td>7–28</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>Tranxene</td>
<td>Anxiolytic-S/H</td>
<td>3.75–22.5/7.5–15</td>
<td>—</td>
<td>30–60</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Valium</td>
<td>Anxiolytic-S/H, SKR, anticonvulsant</td>
<td>2–40/5–10</td>
<td>0.5–2.0 mg/dl</td>
<td>20–90</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Dalmane</td>
<td>Hypnotic</td>
<td>—/15–30</td>
<td>0.25 mg/dl</td>
<td>24–100</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Ativan</td>
<td>Anxiolytic-S/H, anticonvulsant</td>
<td>0.5–3.0/2–4</td>
<td>0.3 µg/dl</td>
<td>10–20</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Serax</td>
<td>Anxiolytic-S/H</td>
<td>10–120/10–30</td>
<td>3–5 mg/l</td>
<td>5–10</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Restoril</td>
<td>S/H</td>
<td>—/7.5–30</td>
<td>1.0 mg/l</td>
<td>9–12</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Halcion</td>
<td>Anxiolytic-S/H</td>
<td>0.25–1.5/0.125–0.5</td>
<td>7 µg/kg (toxic dose)</td>
<td>2–3</td>
</tr>
</tbody>
</table>

*Note: S/H = sedative/hypnotic; SKR = skeletal muscle relaxant.*
Mechanism of toxicity
Mechanism of toxicity

- When a benzodiazepines binds to its receptor site at GABA at the alpha-gamma subunits, it causes a conformational change in the receptor complex, enhancing the binding of GABA neurotransmitter to its own receptor site on the beta subunit.
- Benzodiazepines potentiate GABA’s inhibitory effect by facilitating GABA binding and increasing the frequency of chloride ion channel opening, further hyperpolarizing the cell.
- The effects of GABA-mediated actions account for benzodiazepines’sedative/hypnotic, anticonvulsants, and skeletal muscle relaxation properties.
- At high doses, benzodiazepines induce neuromuscular blockade and cause vasodilation and hypotension.
Toxic dose of benzodiazepines

• In general, the toxic:therapeutic ratio for benzodiazepines is very high.
• For example, oral overdoses of diazepam have been reported in excess of 15-20 times the therapeutic dose without serious depression of consciousness.
• On the other hand, respiratory arrest has been reported after rapid IV injection diazepam, midazolam, and many other benzodiazepines.
• Also, ingestion of another drug with CNS-depressant properties (e.g. barbiturates, ethanol, opioids, etc) will likely produce additive effects.
Signs and symptoms of acute toxicity

- Signs and symptoms of benzodiazepines overdose are nonspecific.
- CNS depression can range from mild drowsiness to coma.
- Mild toxicity is characterized by ataxia, drowsiness, and motor incoordination.
- In moderate toxicity, the patient aroused by verbal stimulation and may enter coma.
- Patients in severe toxicity are unresponsive except to deep pain stimulation.
- In general, respiratory depression and hypotension are rare.
### Clinical presentation of benzodiazepine toxicity

<table>
<thead>
<tr>
<th>Central Nervous System</th>
<th>Neuromuscular</th>
<th>Cardiovascular</th>
<th>Respiratory</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>Slowed voluntary movements</td>
<td>Mild depression in heart rate and blood pressure possible</td>
<td>Mild respiratory depression</td>
<td>Nausea</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Ataxia</td>
<td></td>
<td>Respiratory depression may be more pronounced after IV administration</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>Hypotonia</td>
<td></td>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
<td></td>
<td></td>
<td>Incontinence</td>
</tr>
<tr>
<td>Impaired cognition</td>
<td></td>
<td></td>
<td></td>
<td>(all rare)</td>
</tr>
<tr>
<td>Delirium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low grade coma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare cyclic coma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterograde amnesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical management of acute overdose

- Clinical management is symptomatic.
- Efforts initially should be addressed toward reducing absorption, thereafter, therapy largely supportive.

  **Benzodiazepine antidote**

- Flumazenil is a benzodiazepine antagonist.
- This antidote is structurally similar to benzodiazepines and binds at the same site within the neuron.
- When it binds to the neuron, it displaces benzodiazepines without triggering the change in chloride channels caused by active benzodiazepines.
- Flumazenil completely reverses the sedative, anxiolytic, anticonvulsant, ataxic, anesthetic, comatose, and muscle relaxant effects.
Treatment of benzodiazepines toxicity

1. Airway
   Suction
   Check gag reflex
   Evaluate posterior tongue displacement
   Intubate if necessary

2. Breathing
   Determine hypoventilation, hypercarbia
   Assess oxygenation
   Assess possible aspiration
   Intubation with mechanical ventilation if necessary

3. Circulation
   Assess volume depletion or vasodilation
   Fluid and dopamine if necessary

4. Other
   Assess hypoglycemia
   Activated charcoal
   Assess other causes of coma

5. Flumazenil
   Indications: history of benzodiazepine overdose
   Contraindications: (a) history of seizures, (b) chronic use of
   benzodiazepine and potential for withdrawal, (c)
   suspected co-ingestion of epileptogenic agent,
   e.g., cyclic antidepressant, phenothiazine, cocaine

Dose:
   Adults: slowly titrate up to 0.5–5 mg
   Children: slowly titrate to 0.005–0.2 mg/kg
Tolerance and withdrawal

- Cross tolerance to barbiturates and alcohol has been noted with benzodiazepines.
- The withdrawal syndrome is not as severe in the barbiturates and is slower in onset (as long as 2 weeks).
- Flumazenil administration can precipitate acute withdrawal in benzodiazepine-addicted individuals.
- As with barbiturates and alcohol, benzodiazepines withdrawal signs and symptoms are similar and include tachycardia, hypertension, diaphoresis, agitation, mental status changes, and seizures.
- Treatment is with diazepam or phenobarbital.
Which are safer, barbiturates or benzodiazepines?

- Benzodiazepines are generally safer than barbiturates, producing less respiratory depression and minimal cardiac effects. Death from isolated benzodiazepine overdose is extremely rare.
- Benzodiazepines increased therapeutic index, relative to barbiturates, and lack of anesthetic properties have promoted the substitution of benzodiazepines for barbiturates.
CNS STIMULANTS

What are amphetamines?

• They are synthetic stimulant agents with sympathomimetic properties.
• Amphetamines act on both the central nervous system (CNS) and the peripheral nervous system.
• Chemically, they are structured like adrenaline (epinephrine), stimulating both alpha and beta receptors.
• Amphetamines and their derivatives are indirect agonists that mimic the actions of epinephrine and norepinephrine. The agents either stimulate release of, or block the reuptake of naturally occurring sympathomimetics.
Common amphetamine like drugs

- Amphetamine was synthesized in the late 1920s and has a large number of analog including:
  - Methamphetamine (slang names: ice, glass, crank).
  - Methylphenidate (Ritalin).
  - Methylenedioxymethamphetamine (MDMA, “ecstasy”).
  - 3,4-methylenedioxymethamphetamine (MDA, ‘harmony’).
  - A closely related natural alkaloid, cathinone, is found in khat, a plant that produces effects indistinguishable from those of amphetamines.

Therapeutically used for anorexia, bronchodilation, improved cerebral circulation, improved attention span, alertness, wakefulness (narcolepsy) and hyperkinetic children (ADHD).
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Clinical Indications</th>
<th>Typical Adult Dose (mg)</th>
<th>Half-Life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzphetamine</td>
<td>Anorectant</td>
<td>25-50</td>
<td>6-12</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>Anorectant</td>
<td>15</td>
<td>17-20</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>Narcolepsy, hyperactivity (children)</td>
<td>5-15</td>
<td>10-12</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>Anorectant</td>
<td>25, 75 (SR⁶)</td>
<td>2.5-6</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>Anorectant</td>
<td>20-40</td>
<td>10-30</td>
</tr>
<tr>
<td>Mazindol</td>
<td>Anorectant</td>
<td>1-2</td>
<td>10</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Narcolepsy, hyperactivity (children)</td>
<td>5-15</td>
<td>4-5</td>
</tr>
<tr>
<td>Methylenedidate</td>
<td>Hyperactivity (children)</td>
<td>5-20</td>
<td>2-7</td>
</tr>
<tr>
<td>Pemoline</td>
<td>Narcolepsy, hyperactivity (children)</td>
<td>18.7-75</td>
<td>9-14</td>
</tr>
<tr>
<td>Phendimetrazine</td>
<td>Anorectant</td>
<td>35, 105 (SR⁶)</td>
<td>5-12.5</td>
</tr>
<tr>
<td>Phenmetrazine</td>
<td>Anorectant</td>
<td>25, 75 (SR⁶)</td>
<td></td>
</tr>
<tr>
<td>Phentermine</td>
<td>Anorectant</td>
<td>8, 30 (SR⁶)</td>
<td>7-24</td>
</tr>
</tbody>
</table>

⁶See also Table II-32, p 248 (LSD and other hallucinogens).
⁷Half-life variable, dependent on urine pH
⁸Withdrawn from the US market September 1997.
⁹SR = Sustained-release formulation.
Common effects of the sympathomimetic agents such as amphetamines

Amphetamines produce the “fight or flight” responses:

- **CNS**: increased in mental activity, hallucination, seizures.
- **Respiratory**: bronchodilation.
- **Cardiovascular**: tachycardia, hypertension.
- **GIT**: increased in peristalsis.
- **Papillary**: dilation mydriasis.
- **Glands**: increased sweating, dry mouth.
- **Basic metabolite**: increases hyperthermia.
Mechanism of toxicity

• Unlike the naturally occurring sympathomimetics, the amphetamine compounds are weak bases that are well absorbed orally.

• Amphetamine compounds activate the sympathetic nervous system via:
  - Central nervous system stimulation (analeptic).
  - Peripheral release of catecholamines.
  - Inhibition of neuronal reuptake of catecholamines.

• Amphetamines also inhibit monoamine oxidase (MAO), which degrades catecholamine neurotransmitters intracellularly.

• The net effect is an increase of neurotransmitter release into the synapse.
Illustration of the mechanism of amphetamine action

**NORMAL**

Pre-synaptic vesicles release neurotransmitters into synapse; NT bind post-synaptic receptors; NT return to pre-synaptic side.

**AMPHETAMINE**

Amphetamine enters vesicles; enhances leakage of NT; amphetamine also inhibits MAO $\rightarrow$ reduced NT catabolism.

- ○ Vesicles
- ▴ Neurotransmitters
The major cardiovascular symptoms associated with amphetamine toxicity?

- Chest pain
- Palpitations/tachycardia
- Cardiomyopathy
- Myocarditis
- Hypertension
- Myocardial infarction
- Arrhythmia
- Sudden death
How should amphetamine-induced cardiotoxicities be managed?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension/agitation</td>
<td>Minimize stimulus.</td>
</tr>
<tr>
<td></td>
<td>Administer sedation agents (benzodiazepines), calcium channel blockers, IV</td>
</tr>
<tr>
<td></td>
<td>nitroprusside.</td>
</tr>
<tr>
<td>Chest pain (due to direct cardiac toxicity [myocarditis], vasospasm,</td>
<td>Administer benzodiazepines, nitroglycerin, morphine, or aspirin.</td>
</tr>
<tr>
<td>thrombus formation)</td>
<td></td>
</tr>
<tr>
<td>Palpitations/dysrhythmia</td>
<td>Benzodiazepines, calcium channel blockers, lidocaine as needed</td>
</tr>
<tr>
<td></td>
<td>Correct hypoxia and electrolytes.</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Diuretics, digoxin, and afterload reduction.</td>
</tr>
</tbody>
</table>

Beware of beta blockers; resultant unopposed alpha effects can produce intense vasospasm and paradoxical hypertension. Avoid use of beta blockers.
The major neurologic signs and symptoms associated with amphetamine toxicity

- Anxiety/agitation
- Delirium/hallucinations
- Aggression/hyperactivity
- Euphoria
- Headache
- Seizure
- Talkativeness
- Cerebral hemorrhage/edema (owing to hypertension or cerebral vasculitis).
How should amphetamine-induced neurotoxicities be managed?

Management of Amphetamine-induced Neurotoxicities

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation, aggression, hallucination</td>
<td>Benzodiazepines, antipsychotic agents (Haldol), minimize external stimuli, physical restraints (when necessary)</td>
</tr>
<tr>
<td>Seizures</td>
<td>Benzodiazepines, phenobarbital</td>
</tr>
<tr>
<td>Headache, cerebral hemorrhage, stroke</td>
<td>Correction of hypertension, neurosurgical intervention</td>
</tr>
</tbody>
</table>
Other systemic toxicities, and their treatments, secondary to amphetamine use.

- Hyperthermia: rapid cooling measures, spray mist, ice, dantrolene.
- Rhabdomyolysis: control hyperthermia, alkalization, calcium replacement, fluids, diuretics, mannitol.
- Renal failure: treat rhabdomyolysis, hemodialysis.
- Anorexia/weight loss: psychologic/psychiatric intervention.
Complications

- Because amphetamines often are synthesized in poorly controlled settings, individuals with amphetamine intoxication may experience concomitant toxic exposures. Lead, other metals, organic solvents, and precursor molecules all have been found in amphetamine samples and blood of individuals with amphetamine toxicity.
- Obstetric complications: amphetamines can cross the placental fetal blood barrier and may cause contractions, decreased fetus blood flow, intrauterine demise and abortion.
- Complications of IV drug abuse (endocarditis, HIV, cellulites).
• Tolerance and an accompanying psychological dependence can lead to escalating use of the drug and increased toxicity.

• Chronic use can lead to a depletion of catecholamines stores and a paradoxical reverse effect of the drug—a wash out.

• Amphetamine drug withdrawal symptoms include: agitation, anxiety, craving drugs, depression, exhaustion, fatigue, increased appetite, irritability, lethargy, loss of pleasure, mood swings, paranoia, sleep disturbance, suicidal ideation.
Can amphetamine use be diagnosed in the laboratory?

- A qualitative urine drug screen may detect typical amphetamines for up to 72 hours after use.
- Newer hallucinogenic amphetamines may not be detected.
- A positive test for amphetamines may be masked by adding Drano, bleach, or salt tablets to the urine sample.
- False-positive drug screen can be result from ephedrine, pseudoephedrine, and phenylpropanolamine, which are found in several over-the-counter medications.
COCaine TOXICITY

• Cocaine is derived from the dried leaves of the plant *Erythroxylon coca*.

• In the early 1900s, cocaine was an important ingredient in Coca-Cola. The drink was originally sold medicinally as a “brain tonic.”

• Cocaine is the most popular drugs of abuse. Before it arrives on the street, the crystalline form of the drug is diluted (cut) with a diluent, such as lactose, mannitol, sucrose, procaine, or lidocaine.

• The substance is injected IV (10 to 20 % solution), administered by intranasal insufflation (snorted as 50 to 75% powder), or burned and inhaled as the freebase (*crack* cocaine, 20% powder).
The biological effects of cocaine

- Cocaine is a sympathomimetic.
- Cocaine displays reversible CNS and peripheral actions.
- It possesses local vasoconstrictor actions.
- It inhibits the reuptake of epinephrine and norepinephrine in peripheral ganglia.
- It increases release of norepinephrine and inhibits reuptake of dopamine and serotonin in CNS.
- Production of euphoria is due, in part, to inhibition of dopamine reuptake in central synapses.
- In addition, cocaine blocks fast sodium channels, stabilizing nerve membranes and producing local anesthesia.
Mechanism of cocaine action

NORMAL

Pre-synaptic

Post-synaptic

Neurotransmitters bind on post-synaptic receptors, release and re-enter pre-synaptic side through carriers.

COCAINENeurotransmitters (serotonin, norapinephrine, dopamine)

Cocaine binds carrier channels; neurotransmitters build up in synapse and on post-synaptic receptors; enhanced neurotransmitter effect.

C = Cocaine
Toxic dose

- Toxic dose is variable and depends on:
  1. Individual tolerance.
  2. The route of administration.
  3. And the presence of other drugs.
- Because of its high toxicity and potential for abuse, its use is limited as a topical anesthetic/vasoconstrictor (1 to 10% solution) for surgical procedures involving the oral and nasal mucosal cavities.
- The usual max. recommended for intranasal local anesthesia is 100-200mg.
- A typical “line” of cocaine to be snorted 20-30 mg or more.
- Ingestion of 1 g or more of cocaine very likely to be fatal.
Pharmacokinetics

The onset of effects, peak effects, duration of euphoria, and plasma half-life for different routes of administration are as follows:

• Inhalation (7 s onset, 1-5 min peak, 20 min duration, 40-60 min half-life)
• IV (15 s onset, 3-5 min peak, 20-30 min duration, 40-60 min half-life)
• Nasal (3 min onset, 15 min peak, 45-90 min duration, 60-90 min half-life)
• Oral (10 min onset, 60 min peak, 60 min duration, 60-90 min half-life)
The effects on the cardiovascular system

- Cocaine produces coronary artery vasospasm and increased platelet adhesion, decreasing the supply of blood and oxygen to myocardial tissue which may lead to myocardial ischemia or infarction (heart attack).
- Most patients who presents with cocaine-associated chest pain will be diagnosed with myocardial infarction.
- It elevates blood pressure and heart rate, increasing myocardial work and demand for oxygen.
- Cocaine can cause also ventricular and supra ventricular arrhythmias and aortic dissection.
- Chronic cocaine use can develop artherosclerosis and cause myocarditis and cardiomyopathy.
- Renal failure may result from shock renal arterial spasm, or rhabdomyolysis with myoglobinuria.
The effects on the central nervous system

- Cocaine causes release of catecholamines in the CNS.
- Central hyperstimulation: initially produce euphoria followed by anxiety, agitation, delirium, psychosis, muscle rigidity or hyperactivity and seizures. High doses may cause respiratory arrest.
- Coma may be caused by postictal state, hyperthermia or intracranial hemorrhage resulting from cocaine-induced hypertension.
- Ischemic and hemorrhagic stroke present as headaches or changes in mental status, often mistaken as psychiatric instability.
- Cerebral vasculitis also has been associated with cocaine use.
Addiction to cocaine is essentially indistinguishable from amphetamine habituation. Because of its rapid metabolism, larger doses of cocaine are required to maintain the euphoric effects in a chronic user.

Cocaine produces a state referred to as “high” leading to strong psychological but little physical dependence.

With chronic cocaine use, insomnia, weight loss, and paranoid psychosis may occur.

A “washed-out” syndrome has been observed in cocaine abusers. Consisting of profound lethargy and deep sleep that may last for several hours to days followed by spontaneous recovery.

Death is usually caused by a sudden fatal arrhythmia, status epilepticus, intracranial hemorrhage, or hyperthermia.
Dose cocaine affect the lungs?

- Smoking crack cocaine can precipitate attacks of asthma or chronic obstructive pulmonary disease.
- Cardiogenic or noncardiogenic pulmonary edema has occurred after cocaine use.
- Severe upper airway burn injury can occur after crack smoking.
- Crack smokers present mouth and pharyngeal pain, drooling, hoarseness, and stridor that begins during an episode of pipe smoking.
- Nasal septal perforation may occur after chronic snorting.
What is “crack dancing”?  

• Episodes of acute dyskinesia have been associated with cocaine use.  
• This presents with choreoathetoid movements of the extremities, lip-smacking, and repetitive eye blinking.  
• This movement disorder may be caused by supersensitivity to the effects of dopamine.

**Fetal effects**  

• Cocaine has been associated with increased risk of spontaneous abortion, abruptio placentae, intrauterine growth retardation, and prematurity.  
• Cocaine causes maternal hypertension, decrease uterine blood flow, and placental vasoconstriction.
Treatment

- Benzodiazepines can be used to treat the major manifestations of cocaine toxicity such as: agitation, cardiovascular instability and neuropsychiatric complications of cocaine toxicity.
- Airway, breathing, and circulation (ABCs) are priorities. Ensure an open airway and maintain adequate ventilation and oxygenation.
- Intravenous diazepam or lorazepam may halt the seizures activity if given in adequate doses. If benzodiazepines are ineffective, intravenous phenobarbital can be used.
- Phenytoin is not an effective or safe antiepileptic in most toxic-induced seizures.
How can one control the body temperature of a hyperthermic cocaine patient?

- Body temperature above 40°C following cocaine use is life-threatening and should be lowered immediately.
- Undress the patient, spray him with a cool mist, and use fans to create a constant air current.
- Apply ice packs and use cool tools and chilled fluids can rapidly lower hyperthermic body temperature.
How to treat ischemic chest pain?

- Oxygen, nitrates, and aspirin are indicated as any other patient with ischemic chest pain.
- Benzodiazepines will inhibit central sympathetic activity and help control hypertension and tachycardia.
- Because cocaine-induced hypertension and coronary vasoconstriction are alpha-mediated phenomena, blocking beta receptors will lead to unopposed alpha effects, increasing myocardial oxygen demand, decreasing oxygen supply, and increasing lethality. Therefore beta-blockers are contraindicated.
- Phentolamine (an alpha-blocker), nitroglycerin, or nitroprusside can be used to treat hypertension.
What are body stuffing and body packing?

- Some patients swallow crack cocaine to avoid having police seize it as evidence. These patients are called “body stuffers”.
- Treatment involves observation, activated charcoal administration, and whole-bowel irrigation with polyethylene glycol solution.
- The “body packer” attempts to smuggle cocaine by wrapping them in plastic bags, etc., and swallowing large numbers. If a package leaks severe toxicity and death can result.
- Surgical removal may be indicated if package ruptured or obstruct the GI tract.
Is there an interaction between cocaine and ethanol?

- The use of more than one drug among the drug abusers is a common practice that had often lead to catastrophic drug-drug interactions.
- When cocaine and ethanol are used together, the active metabolite cocaethylene is formed in the liver. Cocaethylene has effects similar to those of cocaine itself but is longer lasting, more cardiotoxic, and more lethal.
Households Chemicals
Hydrocarbons & Toxic Gases

- Hydrocarbons are ubiquitous products that are easily accessible and result in high morbidity when ingested or aspirated.
- One of the most common causes of fatality from ingestion in children younger than age 5.
- The annual incidence of hydrocarbon exposures in USA is approximately 65,000.
- 95% of these are unintentional, and about 60% involve children.
- Children under age 5 years account for 90% of the reported deaths attributed to hydrocarbon poisoning.
Source of hydrocarbon products

• Many of the ingested hydrocarbon products are compounds resulting from distillation of petroleum or crude oil.

• Other sources of hydrocarbons, including coal, animal fats, plants, and flowers (e.g., turpentine is derived from pine oil) are organic.

• These hydrocarbon products can be classified into:
  - Aliphatic
  - Aromatic
  - Halogenated

• Some hydrocarbons pose unique risks because they have halogen side chains (e.g., carbon tetrachloride) or other inherently toxic compounds, such as heavy metals and insecticides.
Household products containing hydrocarbons

The most common hydrocarbon product exposures:

• Gasoline (33%)
• Freon and propellants (11%)
• Mineral spirits or paint thinner (9%)
• Lubricating and motor oils (7%)
• Lighter fluid or naphtha (7%)
• Kerosene (5%)
## Household products containing hydrocarbons

<table>
<thead>
<tr>
<th>Adhesives (glues)</th>
<th>Laxatives</th>
<th>Paste wax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baby oil</td>
<td>Lighter fluid</td>
<td>Petroleum jelly</td>
</tr>
<tr>
<td>Car wax</td>
<td>Liquid solder</td>
<td>Pine oil</td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>Liquid steel</td>
<td>Plastic cement</td>
</tr>
<tr>
<td>Contact cement</td>
<td>Mineral oil</td>
<td>Solvents</td>
</tr>
<tr>
<td>Furniture polish*</td>
<td>Mineral seal oil*</td>
<td>Stain remover</td>
</tr>
<tr>
<td>Furniture refinisher</td>
<td>Mineral spirits</td>
<td>Sterno fuel</td>
</tr>
<tr>
<td>Gasoline</td>
<td>Mothballs</td>
<td>Stoddard solvent</td>
</tr>
<tr>
<td>Home heating fuel</td>
<td>Motor oil</td>
<td>Turpentine</td>
</tr>
<tr>
<td>Kerosene</td>
<td>Naphtha</td>
<td>Typewriter correction fluid</td>
</tr>
<tr>
<td>Kitchen wax</td>
<td>Paint remover</td>
<td>Varnish remover</td>
</tr>
<tr>
<td>Lacquer</td>
<td>Paraffin</td>
<td>Wax</td>
</tr>
</tbody>
</table>
Aliphatic hydrocarbons

- There are some 28,000 cases of accidental poisonings, yearly, in children under the age of five.
- Deaths due to the petroleum distillate ingestion account for 12-25% of the total poison-related deaths in children.
- Most commonly ingested hydrocarbons, in order of frequency of occurrence, are:
  - Kerosene
  - Mineral seal oil preparations
  - Turpentine
  - Gasoline
  - Lighter fluids
  - Petroleum-based insecticides.
Toxicity

Occupational and environmental exposures to solvents and vapors are very common. Additionally, accidental and intentional exposure to solvents also occurs.

• Factors affecting toxicity include:
  1. Surface tension
  2. Viscosity
  3. Volatility
  4. Lipid solubility
  5. Solvent properties

• Severity of the toxic effects varies according to the exposure conditions and the nature of the chemical. Most exposures occur via inhalation.
## Toxicity of components of petroleum

<table>
<thead>
<tr>
<th>Component</th>
<th>Volatile</th>
<th>Viscous</th>
<th>CNS Toxicity</th>
<th>Pulmonary Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gases</td>
<td>Y</td>
<td>N</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>Benzinene</td>
<td>Y</td>
<td>N</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>Gasoline</td>
<td>Y</td>
<td>N</td>
<td>High</td>
<td>Mod.</td>
</tr>
<tr>
<td>Naphtha</td>
<td>Y</td>
<td>N</td>
<td>High</td>
<td>Mod.</td>
</tr>
<tr>
<td>Kerosene</td>
<td>N</td>
<td>N</td>
<td>Mod.</td>
<td>High</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>N</td>
<td>N</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>Lubricants</td>
<td>N</td>
<td>Y</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Gasoline

- Complex mixtures of hydrocarbons (C4 to C12) also contain benzene, antiknock agents, antioxidants, rust inhibitors, and dyes.
- If abused, causes euphoria, which may last for several hours.

**Acute toxicity**

**Oral:** loss of gastrointestinal epithelium, GI irritation (nausea, vomiting & diarrhea).

**Inhalation:** cardiovascular sensitization to circulating catecholamines leads to increased heart rate and respiration, pulmonary edema, pneumonitis, seizures, fibrillation, coma, death.
Chronic toxicity

Neuropsychological effects (motor and cognitive impairment).

Treatment: (acute toxicity)

- Oral ingestion: nasogastric lavage; oils (olive/mineral oil); prophylactic treatment (steroids & antibiotics).
- Induced vomiting contraindicated.
- Inhalation: supportive and symptomatic.
**Halogenated aliphatic hydrocarbons**

**Carbon tetrachloride**

- Once widely used as a dry-cleaning chemical, degreasing agent, fire extinguisher, and for the manufacture of chlorofluoromethane.

- The use of carbon tetrachloride is now limited mostly to laboratory and industrial applications.

- Cause hepatorenal toxicity.
Carbon tetrachloride toxicity

Acute toxicity

• Stage 1 (shortly after exposure):
  nausea, vomiting, abdominal pain, CNS and respiratory depression, ventricular fibrillation.
• Stage 2 (several hours to 2-3 days):
  Hepatic damage (elevated hepatic serum enzymes).
• Stage 3 (two weeks):
  Renal effects (reduced blood flow, reduced glomerular filtration, oliguria).

Chronic toxicity

Dermititis, hepatic damage (cirrhosis, hepatoma), anemia (aplastic anemia).
Metabolism

- Toxicity of carbon tetrachloride is due to its metabolites such as: trichloromethyl free radical (by Cyt P450), and phosgene, which are unstable and covalently bind to macromolecules such as proteins and lipids (lipid peroxidation).

Treatment

- Supportive and symptomatic (acute toxicity).
- Renal failure: dialysis.
- Anemia: not treatable.
Aliphatic alcohols

Methyl alcohol

- Methyl alcohol, or methanol, is a widely used solvent and is found in paint removers, varnishes, and cleaning solutions.
- It is also used as an antifreeze fluid.
- Consumed as a cheap alcohol by alcoholic derelicts.
- Fatal dose ranges between 60 and 240 ml.

Acute toxicity
Mild inebriation, drowsiness.

Delayed effects
GI distress, acidosis, blurred vision, blindness, difficulty in breathing, respiratory depression, coma.
Metabolism

- Methanol converted to formaldehyde by alcohol dehydrogenase.
- Formaldehyde causes irritation and tissue damage.

Characteristic odor (diagnostic):
Urine has the smell of formaldehyde.

Treatment

- Lavage
- Ethanol
- Bicarbonate
- Hemodialysis
Aromatic hydrocarbons

Benzene

• Colorless, volatile liquid with a pleasant odor.
• It is found in paints and varnish removers, glue.
• It is used in the manufacture of nylon, styrene, phenol, and detergents.
• Causes aplastic anemia and leukemia (shoes factories workers and tire workers).

Acute toxicity

• Euphoria and other central as well as peripheral effects (such as: dizziness, headache).
• Cardiac effects, respiratory depression, convulsions, coma.
• Mucus membrane irritation, blurred vision, ataxia.
Chronic toxicity

- CNS effects (anorexia, headache, drowsiness, nervousness), Cerebral damage (atrophy).
- Anemia (aplastic anemia).
- Leukemia.
- Lymphomas.
- Chromosomal effects (abnormalities).

**Metabolism**

- Toxicological important metabolites: benzene bioactivated by Cyt P450 into the reactive metabolites: benzene semiquinone and benzene quinone which are covalently bind to proteins, lipids and nucleic acids and induce cellular damage & cancer.
- Treatment (acute effects): Supportive and symptomatic
Carbon monoxide (CO)

- Colorless, odorless, tasteless, non irritating gas.
- Chemical asphyxiants produce toxicity through induction of cellular hypoxia or anoxia (silent killer >3500 death/year).
- **Sources:** Natural: ocean (microorganisms); forest fires.
  Pollution: fossil fuel combustion.
  Other: cigarette smoke; fires.
- **High concentrations:** heavy traffic, underground garages and tunnels; fires.
- **Factors affecting toxicity:**
  1. Decrease barometric pressure (high altitude).
  2. High alveolar ventilation (exercise, excitement).
  3. High metabolic rate (e.g., children).
  4. Preexisting diseases (heart & pulmonary diseases).
CO toxicity

• Clinical presentation of CO poisoning depends on the time of exposure and the concentration of CO in the area.

Acute toxicity

• Headache, dizziness, nausea, vomiting (0.01%)
• Severe headache (0.01-0.05%)
• Arterial fibrillation
• Sinus tachycardia
• Convulsions: coma, death (0.1-0.5%)
• Infants are highly susceptible (fetal hemoglobin has greater affinity for CO). Also individuals with certain diseases.
• Delayed effects (survivors): neuropsychiatric impairments (impaired judgment, abstract thinking, lack of concentration).
Relationship of concentration of CO in air versus the CO in blood
Mechanism of toxicity

1. Less oxygen in the blood (lower conc. of O2 in air).
2. Reduction in oxygen carrying capacity (affinity of CO for hemoglobin is 250x more than that of O2) and the formation of carboxyhemoglobin (COHb).
3. Reduction in the dissociation of oxygen from hemoglobin (less O2 available for cellular uptake and utilization). A leftward shift of the oxyhemoglobin dissociation curve.
5. Mitochondria: binding of CO to cytochromes (blockage of electron transport chain).

Results: Cellular hypoxia
Effect of binding of CO to hemoglobin on the dissociation of O2
Clinical diagnosis

- Cyanotic appearance due to CO-myoglobin (living patients).
- Cherry red blood at autopsy due to CO Hb (dead patient).

Treatment

- Oxygen (100% normbaric: 1 atm of pressure)
- O2 in hyperbaric chambers at 3 atm of pressure) (if available).

Chronic toxicity (firemen, smokers)

- Cardiovascular diseases (arthrosclerosis).
- Fetal toxicity (birth defects, mental retardation).
- Behavioral effects (impaired judgment).
- Neuropsychiatric impairments.
Cyanide

- Cyanide is a rapidly acting agent.
- Hydrogen cyanide gas is used as fumigants (used to destroy the pets in situations were other liquid or sprayed pesticide applications are ineffective).

**Toxicity**

- Increased respiration (hypoxia)
- Convulsions
- Respiratory failure.

**Characteristic odor:** Bitter almond breath

**Mechanism of toxicity**

- High affinity for Fe3+ in cytochrome oxidase.
- Blocks oxygen utilization in mitochondria.
- Inhibits cellular respiration (inhibit electron transport chain and decrease ATP production lead to cell death).
Treatment

- Sodium nitrite (IV)/ Amyl nitrite (inhalant)
- Sodium thiosulfate.
- Oxygen (1 atm of pressure).

Nitrites

- Nitrites induces the formation of methemoglobin.
- Cyanide preferentially binds to methemoglobin over cytochrome oxidase enzyme. This frees the enzyme from inhibition and allows oxidative phosphorylation to resume.

Thiosulfate (sulfur donor)

- Through the reaction catalysed by rhodaneses, thiosulfate binds with cyanide (from the cyanoheemoglobin complex) to form a relatively nontoxic complex, thiocyanate, which is eliminate by renal excretion.