SUBSTANCE ABUSE: Stimulants  
(Cocaine/Amphetamines/PCP/Caffeine)  
John Gualtieri, PharmD  
Clinical Assistant Professor  
Dept. of Experimental and Clinical Pharmacology  
College of Pharmacy, University of Minnesota

OBJECTIVES
1. Describe the pharmacology and pathophysiology of cocaine, amphetamines, PCP and caffeine
2. Be able to recognize the clinical manifestations of cocaine, amphetamines, PCP and caffeine
3. Be familiar with the some of the street drug names associated with the stimulants.
4. Identify potential pharmacotherapeutic and non-pharmacotherapeutic interventions used for the treatment of cocaine, amphetamines, PCP and caffeine intoxication.
5. Identify potential pharmacotherapeutic interventions used for the treatment of the withdrawal from cocaine, amphetamines, and caffeine.

COCAINE
I. AVAILABLE FORMS
   • Cocaine is an alkaloid derived from the leaves of the species Erythroxylon coca, an indigenous plant of Central and South America
   
   **Cocaine hydrochloride**: nasal insufflation, IV, SQ, or IM injection; vaginally, rectally, sublingually.
   
   **Cocaine base or “Crack Cocaine”**: alkaloid form which is used for smoking. “Crack” doesn’t actually burn, but vaporizes resulting in the release of the fat soluble alkaloid which readily crosses the blood-lung and blood-brain barriers resulting in a rapid intense “high” comparable to intravenous cocaine administration. The term “Crack” was applied to this form of cocaine because of the characteristic cracking and popping sounds it makes when burned and smoked.

II. SOCIAL IMPACT

   In the 1970s, cocaine gained and has, thus far, retained the dubious distinction of being the most commonly abused stimulant. A dramatic 15-fold increase in cocaine-toxicity related emergency room visits were reported between 1976 and 1986. In 1985, it was estimated that 30 million people in the USA have used cocaine. Today, approximately 2 million people use cocaine regularly. Beginning in the mid-1980s, “Crack” cocaine has become an increasingly popular drug of abuse owing to its ease of production and rapid and intense drug effect when smoked.

   John Belushi, Chris Farley, Len Bias, and River Phoenix are examples of celebrities whose deaths were linked to heavy drug and/or alcohol abuse with cocaine being one of their primary agents of abuse.

III. STREET DRUG IDENTIFICATION AND ANALYSIS

   **Terms**
   - Nose Candy, Coke
   - Blow
   - Chaz
   - Charlie
   - Snow White
   - Speedball (cocaine mixed with heroin taken IV)
   - Peruvian Lady
   - Crack Cocaine (Candy, Rock, Freebase, Scud, Pebbles, Wash)
Adulterants

• Lactose
• Sodium bicarbonate (“baking soda”)
• Lidocaine
• Procaine
• PCP (Phencyclidine)
• Amphetamines
• Caffeine
• Talc

Cocaine Doses and Quantities

<table>
<thead>
<tr>
<th>Method</th>
<th>ONSET</th>
<th>PEAK</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snorted</td>
<td>10-15 min</td>
<td>15-60 min</td>
<td>60-90 min</td>
</tr>
<tr>
<td>IV or Smoked</td>
<td>15-60 sec</td>
<td>5-10 min</td>
<td>30-60 min</td>
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</table>

Distribution: Cocaine concentrations in the brain may be 20 times higher than in the plasma.

Plasma half-life: 60-90 minutes but may be prolonged after insufflation due to continued absorption through the nasal membranes.

Metabolism: It is rapidly hydrolyzed by plasma and liver cholinesterase to eegonine methyl ester, and it undergoes non-enzymatic hydrolysis to benzoylcegonine. These are the two major metabolites and are eliminated primarily in the urine and are the target compounds for most urine drug screens.

Cocaine metabolites may be detected in the urine 5-10 days after last use.

I. PHARMACOKINETICS

• Absorption is rapid and complete through all mucosal membranes.

IV. PHARMACOLOGY

1. Inhibition of neuronal catecholamine uptake resulting in generalized sympathetic nervous system stimulation.
2. Central nervous system stimulation with release of dopamine.
3. Serotonin release and/or blockade of serotonin reuptake.
4. Inhibition of the fast Na-K channels on neural and cardiac tissues which disrupts phase zero depolarization of the normal action potential resulting in a local anesthetic effect (i.e membrane stabilizing effect). This action lowers the threshold for ventricular arrhythmias.

VI. RANGE OF TOXICITY

The toxic dose is highly variable and depends on individual tolerance and the route of administration. Rapid intravenous injection or smoking may produce transient high brain and heart levels, whereas the same dose swallowed or snorted may produce only euphoria.

• The average dose of cocaine orally which may produce serious intoxication is 500 mg.
• The classic fatal dose is 1 gm., but death has been reported with doses as small as 20 mg intranasally.
VII. MOOD ALTERING EFFECTS

• Euphoria
• Excitement
• Heightened energy
• Increased self esteem

• Enormous self confidence
• Lower anxiety and social inhibitions
• Perceived increase in sexual desire and performance

VIII. TOXICOLOGICAL EFFECTS

Most of the manifestation of cocaine intoxication can be explained by excessive central and systematic neural stimulation. Because of this excessive stimulation, cocaine may cause life-threatening problems in multiple organ systems. Cardiovascular and central nervous system toxicity deserve special attention.

A. Cardiovascular:

COMPLICATIONS FROM ACUTE USE
1. Severe hypertension: may cause hemorrhagic stroke or aortic dissection.

2. Arrhythmia: may result in fatal ventricular tachycardia or fibrillation.

   A. Early Onset Arrhythmias: Likely due to the direct cardiotoxic effect of cocaine on the heart caused by the inhibition of the fast Na-K channels of the myocardial conduction system. This “membrane-stabilizing” effect may result in the sudden onset of potentially fatal arrhythmias. These arrhythmias typically occur early on in the patient’s presentation (1-2 hours post-exposure) and require the inclusion of intravenous sodium bicarbonate as one of the first-line pharmacologic agents in the ACLS treatment guidelines.

   B. Late Onset Arrhythmias: May occur in those patient’s who present with a suspected cocaine-induced myocardial infarction. These late-onset arrhythmias likely occur secondary to post-MI ischemic injury and are not likely due to the direct effect of cocaine on the myocardial conduction system. These arrhythmias typically occur late in the patient’s presentation (4-8 hours post-exposure or post-MI). Pharmacotherapeutic management of late-onset arrhythmias in the post-MI patient typically involves the use of intravenous lidocaine.

3. Myocardial ischemia "Cocaine-related chest pain"
   • May be associated with acute on chronic abuse.
   • Likely a result of a trio of mediators which includes coronary artery spasms, platelet aggregation with thrombus formation, and accelerated atherosclerosis.
   • Can be seen in younger adults (20-30 years of age) and should be used as a "tip-off" to a potential cocaine abuser.

4. SHOCK may be caused by myocardial, intestinal, or brain infarction, hyperthermia, tachyarrhythmias, or hypovolemia produced by extravascular fluid sequestration owing to vasoconstriction.

COMPLICATIONS FROM CHRONIC USE
1. Necrotizing vasculitis leading to the disruption and destruction of the vasculature of multiple organ systems resulting in cerebral infarction and hemorrhage, ischemic coronary artery disease, pancreatitis, and renal failure. May be seen more with IV drug abuse.

2. Cardiomyopathy/Congestive Heart Failure with chronic abuse may be attributed to a diffuse myocardial necrosis similar to catecholamine myocarditis.

B. CNS:
1. Headache, muscle rigidity, tremors or musculoskeletal hyperactivity.
2. Anxiety, agitation, delirium, paranoid psychosis, personality disorder, or anorexia.
2. Seizures, usually brief and self-limited, but may be protracted.
3. Coma resulting from intracranial hemorrhage, postictal state or hyperthermia.
C. Respiratory:
   1. Pulmonary edema
   3. “Crack” Lung
   4. Respiratory arrest
   5. Nasal Septum ulcerations and chronic nose bleeds.

D. Renal
   • May result from shock, renal artery spasm, or rhabdomyolysis with myoglobinuria.

E. Metabolic and other:
   1. Hyperthermia
   2. Rhabdomyolysis
   3. Dehydration
   4. Mydriasis
   5. Diaphoresis
   6. Tetanus

DEATH is usually caused by sudden fatal arrhythmia, status epilepticus, intracranial hemorrhage, or hyperthermia. Hyperthermia is usually caused by seizures and/or muscular hyperactivity in the agitated or convulsing patient and is typically associated with rhabdomyolysis, myoglobinuric renal failure, coagulopathy, and multiple system organ failure.

IX. DECONTAMINATION

Decontamination is not necessary after smoking, snorting, or IV injection. Decontamination for body packers and body stuffers will be discussed under special issues.

   Oral Ingestion:
   1. Gastric lavage, do not induce emesis because of risk of seizures.
   2. Activated charcoal (AC)
   3. Gut emptying following small ingestion is not necessary if AC is given promptly.
   4. See section XII for special issues regarding cocaine body packers and body stuffers

X. TREATMENT

A. Basic life support measures: Assess airway, breathing and circulation; IV access and oxygen administration. Monitor temperature closely and assess need for aggressive cooling measures.

B. CNS:
   1. Agitation
      a. Preferred agent is **Diazepam 5-10 mg IV q5-20 min until sedation achieved**. May be repeated Q 1-4 hours prn.
      b. Other agents include:
         Lorazepam 2-4 mg. IV prn.
      c. **Haloperidol 5 mg IM or IV**; may repeat once after 20-30 minutes and hourly if necessary. It has yet to be demonstrated that the use of haloperidol in the acutely agitated patient increases the probability that seizures will occur or that the “seizure threshold” is lowered.

   2. Seizures
      a. Solitary seizures: agent of choice is diazepam 5-10 mg IV prn. Lorazepam may also be used 2-4 mg IV.
      b. **Status epilepticus; Diazepam 5-10 mg IV bolus** every 10-15 min, to a maximum of 30 mg. If convulsions persist use phenobarbital 10-20 mg/kg at a rate not to exceed 50 mg/min.
C. CARDIOVASCULAR

NOTE: Sedation with a benzodiazepine such as diazepam may alone be adequate to reverse cocaine-induced hypertension and tachycardia by attenuating the sympathomimetic effects of cocaine.

1. Hypertension
   a. Preferred primary treatment is diazepam 5-10 mg IV q5-20 min until sedation achieved. May be repeated Q 1-4 hours prn.
   b. **Symptomatic hypertensive crisis:**
      - Agent of choice is Nitroprusside 0.5 - 10 mcg/kg/minute.
      - Benzodiazepine sedation should be used concomitantly with nitroprusside.
   c. Use of beta-adrenergic blocking agents is discouraged.

2. Tachycardia
   a. Benzodiazepine sedation may alone help to control tachycardia and should be considered a first-line intervention.
   b. Use of beta-adrenergic blocking agents is discouraged.

   • The use of **beta-blockers** in the setting of cocaine toxicity is controversial and for the most part discouraged unless life-threatening complications occur. Beta-adrenergic receptor blockers such as propranolol or esmolol may reduce tachycardia and beta1-adrenergic mediated cardiac output. However, a **paradoxical worsening of hypertension may occur** as a result of unopposed alpha1-adrenergic mediated vasoconstriction as well as the blockade of beta2-mediated vasodilation by propranolol.

   • Phentolamine (5-10 mg IV), an alpha-adrenergic receptor blocker may be given to offset the possible reflex vasoconstriction caused by beta-adrenergic receptor blockade.

   ➢ **Labetalol** provides both alpha and beta-adrenergic blocking effects, and may have a theoretical advantage over other beta-adrenergic blockers to treat cocaine induced hypertension and tachycardia. There is no evidenced base data or published research to support its routine use for treatment of cocaine induced hypertension.

   ➢ **Calcium channel blockers:** There is insufficient data available to support CCB safety and efficacy in the setting of cocaine intoxication.

3. Ventricular Arrhythmias (incidence is rare)
   a. Cocaine has a direct cardiotoxic effect caused by the inhibition of the fast Na-K channels of the myocardial conduction system resulting in potentially fatal arrhythmias. These arrhythmias typically occur early on in the patient’s presentation (i.e. within 1-4 hours). Treatment of these arrhythmias should include the prompt administration of sodium bicarbonate (1-2 mEq/kg intermittent IV bolus) to reverse the Na-K channel inhibition by cocaine.

   b. Its is rare to see rapidly fatal arrhythmias more than 6-8 hours after an exposure to cocaine unless the patient develops signs and symptoms consistent with a myocardial infarction. Arrhythmias that occur following cocaine-induced myocardial infarction are likely due to reperfusion or ischemic injury to the heart. The prophylactic use of lidocaine post-MI is controversial given that both lidocaine and cocaine share Type I antiarrhythmic properties. Some clinicians believe that lidocaine may potentiate cocaine-induced dysrhythmias and possibly seizures. This adverse interaction has not been consistently identified in any evidence based research models.

   **BOTTOM LINE:** Lidocaine should be considered for treating late-onset arrhythmias that develop after suspected cocaine-induced MI. Prophylactic use of lidocaine should be considered post-MI secondary to cocaine intoxication if the patient develops PVCs exceeding 10-13 per min.
c. Supraventricular Tachyarrhythmias can be treated with beta-blockers, such as propranolol or esmolol, if used cautiously, as stated above.

- **Adenosine**, although not rigorously studied in patients with cocaine-induced SVT, may represent a safer alternative to beta-adrenergic blockers.

4. Myocardial ischemia

a. Treatment should follow existing protocol for MI. **Nitroglycerin** is an important early treatment intervention for angina and chest pain from possible cocaine induced MI.

b. Cocaine induced chest pain should be observed and followed up based on patient presentation. Interpretation of ECG tracings and thrombolytic use is controversial.

It should be noted that many young cocaine users in the ED have EKGs that look like ischemia or infarction and even meet criteria for giving thrombolytics. Very few, however, actually rule-in for AMI. Therefore, some clinicians have voiced their reluctance to use thrombolytics to patients with cocaine-associated chest pain on the basis of ECG, unless it was clearly changed from a previous tracing or evolving in a manner consistent with an infarction.

D. METABOLIC

1. **Hyperthermia** (core temperature >39°C or 102°F)
   - Cool water/ice washes in conjunction with fans, cooling blanket. Severe hyperthermia may require paralysis.
   - Aggressive fluid hydration is important due to the frequent occurrence of dehydration in the stimulant intoxicated patient.
   - **Fluid Load:** 10-15 ml/kg  
   - **Fluid Maintenance:** 2-3 ml/kg/hour

2. **Rhabdomyolysis:** Obtain CPK levels. Maintain a high urine output with IV fluids. Alkaline diuresis with sodium bicarbonate may also be necessary. Monitor renal function.

XI. MONITORING

Patients presenting with severe signs and symptoms of cocaine toxicity (i.e., CV & CNS S/Sx as described above) should be admitted to an intensive care unit where they can be closely monitored. A urine drug screen should be obtained to confirm cocaine poisoning and to assess other potential drugs on board. All patients with severe poisoning should have frequent monitoring of EKG, electrolytes, calcium, blood gas determination, CBC, serum CPK (including isoenzymes to R/O MI), urine myoglobin, serum creatinine, BUN, urine output, temperature and vital signs.

XII. SPECIAL ISSUES

A. **Continued use during pregnancy:** Cocaine rapidly crosses the placenta and the immaturity of fetal enzyme systems may allow for cocaine accumulation. Complications include an increased risk of spontaneous abortions, premature labor and delivery, low birth weight babies, and an increased risk of abruptio placentae due to hypertension and vasoconstriction.
   - Neonatal Complications: Neglect abuse, cocaine intoxication secondary to breast feeding, physical dependence to cocaine.

C. **Cocaethylene** is a toxic metabolite formed in the liver when cocaine and ethanol are taken together. Compared to cocaine alone, it is more cardiotoxic, more lethal, longer acting, and produces greater euphoria. It has been shown to significantly reduce ventricular contractility and relaxation.

B. Management of body packers and body stuffers:

- *If cocaine toxicity is unusually prolonged or continues to progress despite initial treatment interventions, then consider possibility of cocaine body or cavity packing of cocaine.*
1. **Body packing** is the act of swallowing containers, condoms, balloons, plastic bags or packages filled with illegal drugs for the purpose of smuggling. The treatment is very controversial. The following approach is recommended:

   a. In asymptomatic patients, obtain an abdominal x-ray for visualization of the bag. The absence of bag opacity on x-ray does not rule out ingestion. Give supportive treatment and observe the patient. Whole bowel irrigation can be performed with PEG electrolyte solution until all containers are passed or accounted for. Surgery is only recommended when signs of intestinal obstruction are present or non-invasive attempts at GI decontamination appear futile.

   b. In symptomatic patients, activated charcoal (1 gm/kg.) should be administered, depending on the patient status multiple dose activated charcoal may be required. An abdominal x-ray for visualization of the bag may also be obtained once the patient is stable. Monitor patient and treat clinical effects of cocaine poisoning as described above.

2. **Body stuffing** is the act of swallowing illegal drugs in an effort to conceal the evidence from an immediate arrest. Body stuffers tend to ingest all drugs at hand and require careful monitoring for potential poly-drug overdose. Body stuffers also tend to be more careless with their ingestion than body packers. Treat asymptomatic body stuffers as described above for body packers, keeping in mind the potential for multiple drug ingestion.

**Clinical Presentation of Early Cocaine Withdrawal**

1. **Crash Phase (2 to 5 days):** Depression, hypersomnia, inactivity, and paranoia.

2. **Craving Phase (5 days to months):** Intense desire to use cocaine; severe bouts of anxiety; depression. Daily living is profoundly disrupted, as the stimulant user’s intense cravings for more drug impairs his/her ability to functional socially with other people or effectively maintain productive work habits. Often times, the intense drive to obtain more drug depletes the user’s financial resources which may in turn lead to criminal activity to obtain more drug or obtain money to by more drug.

**Treatment of Cocaine Withdrawal**

Stimulants have extremely powerful reinforcing properties which explains why there is such a high failure rate among chemical dependency treatment programs treating the cocaine addicted patient. The intense euphoria produced by stimulants, particularly cocaine, promotes an intense psychological dependence. Whether there is true physical withdrawal from stimulants is debatable, but psychological withdrawal is well described. Withdrawal from cocaine or amphetamines is not life-threatening and does not generally require the use of any substitute drugs. Intense psychotherapy and support groups are the most effective treatment interventions for stimulant dependence. Various compounds are currently being investigated as adjunctive treatment modalities to intense psychotherapeutic intervention. The most promising agents for managing cocaine withdrawal appear to be carbamazepine, **bromocriptine**, and **tricyclic antidepressants**. Agents that possess dopamine agonist activity (bromocriptine, amantadine, L-Dopa) have shown promising results in investigational trials in terms of attenuating the cocaine cravings experienced by cocaine dependent individuals. However, the majority of published studies evaluating the use of bromocriptine or amantadine have methodological shortcomings such as small sample sizes, uncontrolled open trials, and lack of appropriate standardized rating scales that recognize distinct reductions in cocaine cravings and abstinence.

Tricyclic antidepressants have been shown to reduce the prevalence of depression following cocaine withdrawal. While there is an expectation that relapse rates will be reduced, studies have found conflicting results. Typically, desipramine 150 mg per day has been used for 6-12 months to help control depression following cocaine withdrawal.
Bromocriptine (Parlodel™) Protocol for Cocaine Withdrawal

A. INDICATION

**Adjunctive therapy** for cocaine dependent individuals suffering from the signs and symptoms of cocaine withdrawal, and whom may be at risk for failing treatment for chemical dependency.

B. MECHANISM OF ACTION

The depletion of dopamine in neural reward pathways secondary to chronic cocaine use may lead to the cocaine withdrawal syndrome following cocaine abstinence. Bromocriptine is a dopamine agonist that may prevent or attenuate the cocaine withdrawal syndrome by restoring dopaminergic activity in the dopamine depleted pathways.

C. DOSAGE

Treatments will be based on clinical response and typically range from 0.625 to 1.875 mg t.i.d orally for 1 to 3 weeks.

D. CONTRAINDICATIONS TO USE

1. History of psychosis.
2. Concurrent use of a neuroleptic agent such as a phenothiazine (thiothixene; Navane™) or butyrophenone (haloperidol; Haldol™).
3. Known hypersensitivity to ergot alkaloid medications.
4. Uncontrolled hypertension
5. Patients less than 15 years of age.
6. Nursing mothers.
7. Concurrent oral contraceptive therapy.
AMPHETAMINES and Other Stimulants

I. AVAILABLE FORMS (most are classified as phenylethylamines)

<table>
<thead>
<tr>
<th>CHEMICAL NAME</th>
<th>STREET NAME</th>
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<tbody>
<tr>
<td>Amphetamine</td>
<td>Speed, Uppers, Blue boys, White Cross, Billy Whiz</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>CRANK, ICE, MET, Crystal MET, Glass</td>
</tr>
<tr>
<td>Ephedrine/Pseudoephedrine</td>
<td>Pseudospeed, street speed, Ma Huang, Herbal Ecstasy, nature’s speed, minithins, white-crosses, pink hearts, poor man’s cocaine</td>
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<tr>
<td>Pheylpropanolamine</td>
<td>Diet Pills, Dexatrim</td>
</tr>
<tr>
<td>Methylenedioxymethamphetamine(MDMA)</td>
<td>X, XTC, Xstasy, Ecstasy, Eve, Dennis the Menace, Disco Biscuits, E, Love Doves</td>
</tr>
<tr>
<td>Methylphenindate</td>
<td>Ritalin</td>
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<tr>
<td>Methcathinone</td>
<td>CAT</td>
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II. SOCIAL IMPACT

The extent of abuse of amphetamines, especially CRANK and Xstasy, is starting to exceed that of cocaine in many areas across the USA, particularly among young middle to upper-class adults and college students. Methamphetamine abuse is growing in popularity because it can be easily manufactured in crude, clandestine chemistry labs using readily available precursors such as ephedrine. Methamphetamine and MDMA also have the added “bonus” of providing hallucinogenic properties for the street drug abuser, an effect that is not readily achieved with cocaine use.

MDMA or “Xstasy” is a favorite drug of abuse at night-clubs and “Rave” parties where intensely loud music is played in a forum of vivid lighting effects and dancing. Ma Huang (“Herbal Ecstasy”) and other ephedrine containing OTC stimulants are also gaining popularity as a ‘legal’ psychostimulants. OTC stimulant abuse has also captured the attention of our national media. A May 1996 issue of People magazine reported the death of a 19 year-old male who used an OTC dietary supplement called Ultimate Xyphoria which contained ephedrine and caffeine. The February 2, 1998 issue of Sports Illustrated contained a special report on the heavy use of pseudoephedrine in the NHL as a performance enhancing agent. NHL trainers estimated that 20% of the league’s players routinely take pseudoephedrine before games.

III. STREET DRUG ANALYSIS

- 10-20% of alleged amphetamines are actually so with the majority of the adulterants consisting of over-the-counter decongestants, primarily ephedrine and phenylpropanolamine. Caffeine is also a common adulterant. With heavy chronic use or overdose, ephedrine and phenylpropanolamine can produce the same types pharmacologic and clinical effects as amphetamines.
- Heavy metal contamination, usually lead, is a significant problem associated with the manufacture of amphetamine products in clandestine laboratories.

IV. PHARMACOLOGY

1. Enhance the release and block the reuptake of catecholamines and may have some direct effect on catecholamine receptors resulting in the stimulation of both alpha- and beta-adrenergic receptors.
2. Promote the release of serotonin and may directly affect central serotonin receptors. This serotonergic activity may be responsible for the hallucinogenic effect of amphetamines.
3. Weak monoamine oxidase inhibiting activity, the significance of which is undefined.
4. Substitutions at different positions of the phenylethylamine molecule alters the clinical effects of amphetamines producing varying degrees of cardiovascular stimulation, anorexia, CNS stimulation, and hallucinatory activity. Methoxyl group substitutions on the phenyl ring of amphetamine-like compounds, especially at the 3,4 position increase the hallucinogenic properties.
V. PATTERNS OF USE

<table>
<thead>
<tr>
<th>Low Dose Maintenance</th>
<th>High Dose Cyclical</th>
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<tbody>
<tr>
<td>Enhanced Physical and Emotional Performance</td>
<td>Euphoria</td>
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<tr>
<td>Counteract fatigue</td>
<td></td>
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<tr>
<td>Weight control</td>
<td></td>
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<tr>
<td>Depression</td>
<td></td>
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<tr>
<td>Athletics</td>
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A. Low Dose Maintenance Use: Clinical Features

- **doses equivalent to 2.5 to 15 mg amphetamine**
  - 1st Phase
    - Relaxed alertness
    - Energetic
    - Assertive
    - Appetite & fatigue disappear
    - Insomnia
  - 2nd Phase
    - Mild dysphoria
    - Tension
    - Irritability

- **doses equivalent to 20-50 mg amphetamine**
  - All effects of lower doses intensified
  - "Driven" rather than "relaxed" alertness
  - Impaired concentration
  - Emotional lability
  - "Forgetfulness"
  - Inappropriately serious
  - Increased talkativeness

B. High Dose Cyclical Use: Clinical Features

- In order to achieve intense “highs” users will go on “speed runs” for days to weeks usually consisting of injectable or smokable amphetamines. Because of the development of acute tolerance, they use increasing amounts of amphetamines during this period, usually without much sustenance or sleep, until they achieve their desired euphoric state.

- **Acute psychosis** resembling paranoid schizophrenia may occur during these binges. Once an amphetamine user experiences psychosis, it is more likely to reoccur, even after prolonged abstinence. Repetitive compulsive disorders often afflict behavior patterns in heavy amphetamine abusers.

- Amphetamine **“Withdrawal Blues”**: After binges, subjects may sleep for prolonged periods (days) and feel hungry and depressed when awake. During this depressed state, the patient has continued cravings for amphetamines.

- **VIOLENCE**: Hyperactivity, suspiciousness, feelings of invincibility, and lability of mood may lead to sudden, unwarranted assaultive behavior and is one of the leading causes of death in heavy amphetamine abusers.
II. TOXICOLOGICAL EFFECTS, TREATMENT, AND MONITORING

• Toxicological emergencies and treatment guidelines are essentially the same as described for cocaine intoxication. Both amphetamines and cocaine can produce sympathetic excess (tachycardia, hypertension, hyperthermia, dehydration) resulting in secondary complications such as cerebral vascular accidents, rhabdomyolysis, renal failure, and disseminated intravascular coagulopathy (DIC).

• Differences in clinical effects between amphetamines and cocaine lie in the frequency with which certain complications occur. Table I outlines which disorders are more frequently associated with cocaine poisoning versus amphetamine poisoning.

### Table I

<table>
<thead>
<tr>
<th>AMPHETAMINES</th>
<th>COCAINE</th>
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<tbody>
<tr>
<td>• Psychosis including visual and auditory hallucinations.</td>
<td>• Angina; Myocardial ischemia</td>
</tr>
<tr>
<td>• Extreme agitation which may lead to violent or suicidal behavior.</td>
<td>• Seizures</td>
</tr>
<tr>
<td>• Morbid hyperthermia</td>
<td>• Pulmonary complications due to higher use by smoking and insufflation.</td>
</tr>
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</table>

**Acute Psychosis (Hallucinations)**

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.

- [**Haldol**]: 0.1-0.2 mg/kg IM or IV over 1 minute. May repeat once after 20-30 minutes and hourly prn].

III. AMPHETAMINE WITHDRAWAL

The withdrawal syndrome associated with the cessation of chronic amphetamine abuse is similar to the clinical manifestations of cocaine withdrawal. Treatment of amphetamine withdrawal consists primarily of intense psychotherapy in a drug rehabilitation or psychiatric care institution. Pharmacotherapeutic intervention should be based on the treatment of symptoms. Patients who are mildly anxious may be managed using sedatives, such as benzodiazepines. Thorazine may be useful for the paranoid and agitated patient. Tricyclic antidepressants have shown in clinical trials to reduce the prevalence of depression following stimulant withdrawal. Desipramine 150 mg a day for a duration of 6-12 months is commonly used.

While possibly affective in attenuating strong cravings for cocaine, dopaminergic agents such as bromocriptine, L-Dopa, or amantadine do not have a role in managing withdrawal from amphetamine-related compounds.
PHENCYCLIDINE/KETAMINE

Street-Drug Terms:

Phencyclidine: *PCP, Angel Dust,* marijuana cigarettes laced with phencyclidine may be called “Primos” or “Clickers”.

- Phencyclidine is commonly smoked but can be snorted, ingested, and injected.
- Phencyclidine is frequently found as an adulterant in a number of other illicit drugs such as marijuana, cocaine, speed, and LSD.

Ketamine: Green, Jet, Vitamin K, Special K, Special LA acid, Super acid, Super C, Purple.

- Ketamine is available as pharmaceutical grade injectables and is usually obtained by theft from veterinary offices.
- Ketamine appears to be gaining popularity for use as a powerful psychomimetic by young adults at “rave” parties.

Mechanism of Toxicity: Dissociative anesthetic that produces generalized loss of pain perception with little or no depression of airway reflexes or ventilation. Phencyclidine and ketamine antagonize the action of glutamate at the NMDA receptor by binding within the ion channel to block Ca2+ influx, which results from glutamate binding. It also has CNS-stimulant, anticholinergic, dopaminergic, opiate, and alpha-adrenergic activity. Some users consider phencyclidine and ketamine as the ideal drugs of abuse because they provide the effects of opiates, cocaine, and LSD all in one drug.

Range of Toxicity (Phencyclidine):

- Usual street dose of phencyclidine is 1 to 6 mg resulting in hallucinations, euphoria, and disinhibition.
- Ingestions of 6 to 10 mg causes toxic psychosis and sympathetic stimulation.
- Doses of 150 to 200 mg may be lethal.

Range of Toxicity (Ketamine):

- Usual dose for anesthesia in animals is 1-2 mg/kg IV or 5-10 mg/kg IM.
- The abuser of ketamine will usually use lower than anesthesia doses in order to remain conscious, yet achieve euphoria and hallucinations. Toxicity generally occurs as doses for anesthesia are exceeded.
- Ketamine powder can also be inhaled (~200 mg), smoked, or ingested (~400 mg).

Clinical Effects:

A. *Mild intoxication* may cause ataxia, sedation, lethargy, euphoria, hallucinations, confusion, agitation, paranoia and occasionally bizarre or violent behavior. Abrupt and dramatic mood swings are often reported. Patients may display vertical, horizontal, and even rotary nystagmus. Patient’s may also display a ‘blank’ stare or dysconjugate gaze.

B. *Severe intoxication* is characterized by intense sympathetic stimulation producing hypertension, rigidity, dystonias, myoclonus, hyperthermia, tachycardia, diaphoresis, convulsions, and coma. Death may occur as a result of self-destructive behavior or as a complication of hyperthermia. Seizures have also been reported. Rhabdomyolysis and secondary renal failure may occur as a result of intense skeletomuscular hyperactivity, seizure, and hyperthermia.

C. Long-term abuse has been associated with schizophrenia.

- **Diagnosis** is suggested by the presence of rapidly fluctuating behavior, vertical nystagmus, and signs of sympathomimetic excess.

Treatment: Primarily supportive as described for cocaine, stimulants, and hallucinogens. Treatment should focus on aggressive sedation and correcting potential hyperthermia.
Caffeine Supplements

I. AVAILABLE FORMS (examples)
   - Vivarin (200 mg)
   - Wigraine (100 mg)
   - 357 Magnum (357 mg)
   - NoDoz (100 mg)

II. SOCIAL IMPACT

   The sale and consumption of caffeine containing products (coffee, tea, soft drinks, chocolate) is a global phenomenon that impacts millions of people daily, and is an integral part of our world economy. Typically, the beverage products contain anywhere from 30 mg to 90 mg caffeine per serving, however, some forms of coffee drinks contain as high as 180 to 200 mg caffeine. Chocolate containing products such as candy or chocolate desserts may contain 2 to 20 mg per serving. The OTC headache medications such as Anacin or Excedrin typically contain 30 to 65 mg caffeine per tablet.

   Major medical complications associated with caffeine use have primarily been linked to the excessive abuse of caffeine supplements usually containing 200 mg caffeine per tablet. Significant morbidity and mortality associated with the abuse of caffeine supplements is often linked to the concurrent administration of the OTC sympathomimetics ephedrine or pseudoephedrine. In 1982, the FDA banned the sale of OTC stimulants containing combinations of caffeine with either phenylpropanolamine, ephedrine, or pseudoephedrine. Currently, only caffeine may be labeled as a stimulant in the United States.

III. PHARMACOLOGY

   - Caffeine is a trimethylxanthine similar to theophylline.
   - Competitive inhibition of adenosine receptors, inhibition of phosphodiesterase, increased intracellular calcium and cyclic AMP, and increased release of endogenous catecholamines.

<table>
<thead>
<tr>
<th>CNS</th>
<th>Stimulation of medullary respiratory centers; generalized enhancement of CNS cellular response to stimulation resulting in increased alertness and concentration as well as mood elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDIOVASCULAR</td>
<td>Positive inotropy and chronotropy typically without profound effects on BP and HR unless a large overdose has occurred. Caffeine causes vasoconstriction of the cerebral vasculature making it a good pharmacologic agent for the treatment of headaches. Conversely, caffeine causes vasodilation of renal vasculature resulting in increased diuresis.</td>
</tr>
<tr>
<td>Gl</td>
<td>Caffeine increases gastric secretions and relaxes smooth muscle tissue, especially at the lower esophageal sphincter resulting in gastric reflux problems (heartburn) in some individuals.</td>
</tr>
</tbody>
</table>

IV. RANGE OF TOXICITY

   Adult
   - Moderate toxicity expected at doses exceeding 1000 mg.
   - Severe toxicity or death possible with doses exceeding 30 to 50 mg/kg, however survival has been reported with a dose of 22 grams after cardiac resuscitation and charcoal hemoperfusion.
   - Death following caffeine overdose is rare given the high incidence of spontaneous vomiting that occurs immediately following ingestion, which likely limits the amount of caffeine available for absorption.

   Children
   - Ingestions exceeding 35 mg/kg may product moderate to severe toxicity.
V. TOXICOLOGICAL EFFECTS

Acute Overdose
Mild to Moderate Toxicity: Nausea, vomiting, tremors, restlessness, tachycardia, and confusion.

Severe Toxicity: Delirium, seizures, supraventricular and ventricular arrhythmias, and hypokalemia. Hypotension may occur as a result of excessive Beta₂-mediated vasodilation.

Chronic Overdose
The syndrome sometimes referred to as “caffeinism” may be occur with high-dose caffeine intake over several days and is often confounded by self-imposed sleep deprivation. This syndrome is characterized by anxiety, nervousness, irritability, tremulousness, muscle twitching, and palpitations.

VI. MONITORING

• Serum electrolytes with close attention to potassium (hypokalemia)
• Continuous heart monitor along with intermittent 12-lead ECGs.
• Serum caffeine levels are usually not routinely available in most hospital labs, however, some hospitals may have this capability along with regional reference labs. Coffee drinkers may have caffeine levels ranging from 1 to 10 mg/L whereas serious intoxication and death has been reported with levels of 80 mg/L.
• Acute overdose patients should be monitored for minimum of 6 to 12 hours in an ER or ICU, where prolonged admission may likely be required should the patient display moderate to severe toxicity.

VII. TREATMENT

A. Decontamination
• Activated charcoal (see use of H2 Blockers and anti-emetics below to help with AC retention)
• Repeat dose activated charcoal every 4 to 6 hours may help enhance caffeine elimination.
• Apply orogastric lavage if patient presents following massive ingestion.

B. GI toxicity
• Given the high incidence of spontaneous vomiting, aggressive antiemetic therapy should be employed to help with the retention of activated charcoal. In addition to using traditional anti-emetics, H2 Antagonists should also be used to suppress the gastric hypersecretion caused by caffeine intoxication.
  
  **Ranitidine:** 50 mg IV q6-8 hours.  
  **Metoclopramide:** 10 to 50 mg IV  
  **Odansetron:** 0.6 mg/kg IV

C. Cardiotoxicity
• Beta-blockers are effective in reversing the excess beta-adrenergic stimulation caused by caffeine.
• Although propranolol should be effective at reversing beta-adrenergic toxicity, esmolol is the preferred agent to use given its short elimination half-life and its cardioselectivity.
  
  **Esmolol:** Start with an infusion of 50mcg/kg/min and titrate to effect using a 10 mg/mL solution.
  
  • Adenosine, verapamil, and propranolol may be effective in managing caffeine-induced tachyarrhythmias.

D. Neurotoxicity

  **Solitary seizures:** agent of choice is diazepam 5-10 mg IV prn. Lorazepam may also be used 2-4 mg IV.
**Status epilepticus**: Diazepam 5-10 mg IV bolus every 10-15 min, to a maximum of 30 mg. If convulsions persist use phenobarbital 10-20 mg/kg at a rate not to exceed 50 mg/min.

E. Enhanced Elimination

- Although there is no definitive evidence that **multiple-dose activated charcoal** (MDAC) enhances caffeine elimination, its use is still recommended to help eliminate any theophylline that is generated. MDAC has been shown to effectively enhance the total body elimination of theophylline.
- **Hemodialysis** will greatly enhance total body elimination of caffeine, and should be used in the seriously intoxicated patients or patients with serum caffeine concentrations exceeding 100 mcg/mL.
- Even though charcoal hemoperfusion will also greatly enhance caffeine elimination, its use is not recommended given that it has a higher rate of complications when compared to hemodialysis, and its efficacy is essentially the same.

VII. **CAFFEINE WITHDRAWAL**

Caffeine has the potential to produce tolerance, which means that increased amounts of the drug are needed to achieve a consistent effect. Withdrawal symptoms can occur when use of caffeine is stopped abruptly. Users may experience fatigue, and most commonly, headaches. Primary withdrawal effects last for only a few days although mild withdrawal effects can last as long as a week or two.

- Headaches, fatigue, agitation, craving, and inability to focus.

**REFERENCES**

**Cocaine and Amphetamines**

- Kalant H. The pharmacology and toxicology of ‘ecstasy’ (MDMA) and related drugs. CMAJ 2001; 165(7): 917-928.

**Phencyclidine**


**Caffeine**


**Substance Withdrawal**