Central Nervous System
Stimulants
Objectives:

- Central nervous system (CNS) stimulants
- Types of central nervous system (CNS) stimulants
- What is cocaine?
- How does cocaine produce its effects?
- Illicit Cocaine Production
- Analysis illicit Coca products
- Metabolism and excretion
- Analysis of cocaine and its metabolites in the urine
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Central nervous system (CNS) stimulants, also called psychomotor stimulants or uppers, are a class of drugs that speed up physical and mental processes. They temporarily make patients feel more alert and improve mood. **Stimulants** are typically used to treat medical conditions such as attention-deficit hyperactivity disorder (ADHD), attention-deficit disorder (ADD), fatigue, and narcolepsy. Some stimulants have been used as appetite suppressants, although the safety of this use remains controversial.
Examples of CNS stimulants include

- amphetamines, such as methylphenidate (Ritalin®),

- methamphetamine (e.g. Desoxyn® or Desoxyn Gradumet®),

- caffeine (e.g. coffee or tea),

- nicotine (cigarettes or cigars), and

- the illegal drug cocaine.
Side effects of stimulants vary depending on the specific dose and type of drug. In general, side effects of short-term use may include anxiety, insomnia, dry mouth, depersonalization, feeling of euphoria, increased heartbeat, crying, dysphoria, decreased appetite, hyperventilation, irritability, depression, nervousness, paranoia, mood swings, restlessness, and shaking or trembling.
Most CNS stimulants are highly addictive. However, some newer drugs, such as modafinil (Provigil®) are less addictive. Because stimulants are highly addictive and have euphoric effects on the brain, they are often abused and taken as recreational drugs. Long-term abuse of stimulants can cause changes in the brain and lead to serious health problems, including severe mental illness and memory loss.
types of central nervous system (cns) stimulants

**Schedule I stimulants**: Schedule I stimulants, including aminoxaphen (Aminorex®), cathinone, fenethylline (Captagon®), methcathinone, methylaminorex, and amphetamine variants (e.g. 3,4-methylenedioxymethamphetamine), have no medicinal value and have a high potential for abuse. Therefore, these drugs are not prescribed for medical conditions.

**Schedule II stimulants**: Schedule II stimulants also have a high abuse potential. Patients are likely to become psychologically and/or physically dependent on these drugs. Unless it is an emergency, prescriptions for schedule II stimulants must be made in writing and signed by a healthcare professional. If it is a medical emergency, the healthcare professional must provide written confirmation of the verbal prescription within 72 hours. Prescriptions for schedule II stimulants cannot be renewed. Examples of schedule II stimulants include dextroamphetamine (Dexedrine®), methamphetamine (Desoxyn®), methylphenidate (Ritalin®), phenmetrazine (Preludin®), and biphetamine. An illegal drug, called cocaine, also falls under this category.
**Schedule III stimulants:** Schedule III drugs are less likely to be abused than schedule I and II drugs. Healthcare professionals can give oral or written prescriptions and up to five renewals within six months. Examples of class III stimulants include benzphetamine (Didrex®), chlorphentermine, clortermine, and phendimetrazine tartrate (Plegine® or Prelu 2®).

**Schedule IV stimulants:** Schedule IV stimulants are less likely to be abused than schedule III stimulants. Healthcare professionals can give oral or written prescriptions and up to five renewals within six months. Examples of schedule IV stimulants include armodafinil (Nuvigil®), norpseudoephedrine, diethylpropion hydrochloride (Tenuate®), fencamfamin, fenproporex, phentermine (Fastin®, Lonamin®, or Adipex®), mazindol (Sanorex® or Mazanor®), mefenorex, modafinil (Provigil®), pipradrol, and sibutramine (Meridia®).

**Schedule V stimulants:** Schedule V stimulants, includes one class of drugs called pyrovalerone. These drugs are less likely to be abused than class IV stimulants. These drugs are regulated by the state. In some areas, a prescription may not be needed.
Uses

Appetite suppressant: Examples of these drugs include dexfenfluramine, sibutramine, phentermine, fenfluramine, mazindol, diethylpropion, and fenproporex. However, stimulants cause limited weight loss because patients eventually develop tolerances to long-term treatment.

Attention disorders: Amphetamines, including methylphenidate (Ritalin®), dextroamphetamine (Dexedrine® or Dextrostat®), dextroamphetamine sustained-release capsules (Dexedrine Spansules®), benzphetamine (Didrex®), and lisdexamfetamine (Vyvanse®), are prescription medications that are taken by mouth to treat attention-deficit hyperactivity disorder (ADHD) and attention-deficit disorder (ADD).

Narcolepsy: Patients with narcolepsy, a condition that causes individuals to have sudden attacks of deep sleep or the uncontrollable desire to sleep, also receive stimulants. These drugs help narcoleptic patients stay awake during the day. Modafinil (Provigil®), a newer stimulant, is less addictive and better tolerated than other older types of stimulants. However, some patients need treatment with methylphenidate (Ritalin®) or other types of amphetamines.
**Fatigue:** Caffeine is a stimulant that is found in coffee and various teas, soft drinks, and energy drinks. Methylphenidate (Ritalin® or Concerta®) has also been suggested as a possible treatment for chronic fatigue syndrome (CFS).

**Recreational drug use:** Many stimulants are used recreationally, for no medical purpose. However, abusing stimulants can lead to serious and potentially life-threatening health conditions.

For instance, nicotine is a stimulant that is found in tobacco products, such as cigarettes or cigars. The nicotine makes patients temporarily feel good or energized after smoking. Although this stimulant is legal, it can cause serious health problems, including cancer and emphysema.

Crack is an unprocessed form of cocaine. Crack is cocaine that has not been neutralized to make the hydrochloride salt. This form of cocaine looks like a rock crystal. Individuals typically heat crack and inhale the vapors.
Cocaine
What is cocaine?

Cocaine is a powerfully addictive stimulant that directly affects the brain. Cocaine has been labeled the drug of the 1980s and '90s, because of its extensive popularity and use during this period. However, cocaine is not a new drug.

In fact, it is one of the oldest known drugs. The pure chemical, cocaine hydrochloride, has been an abused substance for more than 100 years, and coca leaves, the source of cocaine, have been ingested for thousands of years.

Pure cocaine was first extracted from the leaf of the *Erythroxylon coca* bush, which grows primarily in Peru and Bolivia, in the mid-19th century. In the early 1900s, it became the main stimulant drug used in most of the tonics/elixirs that were developed to treat a wide variety of illnesses. Today, cocaine is a Schedule II drug, meaning that it has high potential for abuse, but can be administered by a doctor for legitimate medical uses, such as a local anesthetic for some eye, ear, and throat surgeries.
There are basically **two chemical** forms of cocaine: the **hydrochloride salt** and the "**freebase.**"

**The hydrochloride salt**, or powdered form of cocaine, dissolves in water and, when abused, can be taken intravenously (by vein) or intranasally (in the nose). **Freebase** refers to a compound that has not been neutralized by an acid to make the hydrochloride salt. **The freebase form of cocaine is smokable.**

Cocaine is generally sold on the street as a fine, white, crystalline powder, known as "coke," "C," "snow," "flake," or "blow." **Street dealers generally dilute it with such inert substances as cornstarch, talcum powder, and/or sugar, or with such active drugs as procaine (a chemically-related local anesthetic) or with such other stimulants as amphetamines.**
How is cocaine used?

The principal routes of cocaine administration are oral, intranasal, intravenous, and inhalation. The slang terms for these routes are, respectively, "chewing," "snorting," "mainlining," "injecting," and "smoking" (including freebase and crack cocaine).
How does cocaine produce its effects?

A great amount of research has been devoted to understanding the way cocaine produces its pleasurable effects, and the reasons it is so addictive.

One mechanism is through its effects on structures deep in the brain.

Scientists have discovered regions within the brain that, when stimulated, produce feelings of pleasure.

One neural system that appears to be most affected by cocaine originates in a region, located deep within the brain, called the ventral tegmental area (VTA).

Nerve cells originating in the VTA extend to the region of the brain known as the nucleus accumbens, one of the brain's key pleasure centers.

In studies using animals, for example, all types of pleasurable stimuli, such as food, water, sex, and many drugs of abuse, cause increased activity in the nucleus accumbens.
Cocaine in the brain - In the normal communication process, dopamine is released by a neuron into the synapse, where it can bind with dopamine receptors on neighboring neurons.

Normally dopamine is then recycled back into the transmitting neuron by a specialized protein called the dopamine transporter.

If cocaine is present, it attaches to the dopamine transporter and blocks the normal recycling process, resulting in a build-up of dopamine in the synapse which contributes to the pleasurable effects of cocaine.
What are the short-term effects of cocaine use?

- Increased energy
- Decreased appetite
- Mental alertness
- Increased heart rate
- Increased blood pressure
- Constricted blood vessels
- Increased temperature
- Dilated pupils
What are the long-term effects of cocaine use?

- Irritability
- Mood disturbances
- Restlessness
- Paranoia
- Auditory hallucinations
What are the medical complications of cocaine abuse?

• **Cardiovascular effects**
  • disturbances in heart rhythm
  • heart attacks

• **Respiratory effects**
  • chest pain
  • respiratory failure

• **Neurological effects**
  • strokes
  • seizures
  • headaches

• **Gastrointestinal effects**
  • abdominal pain
  • nausea
Illicit Cocaine Production

A. Illicit Natural Cocaine

Production of illicit natural cocaine involves three steps:

• Extraction of crude coca paste from the coca leaf;

• Purification of coca paste to coke base; and

• Conversion of coke base to cocaine hydrochloride
Coca Paste

There are currently two general methods for processing coca leaves into coca paste, hereafter referred to as the **solvent extraction technique** and the **acid extraction technique**.

**The solvent technique** (the traditional methodology) was directly derived from one of the original commercial processes developed in the early 20th century, and remains the most commonly used method in Peru, Colombia, and Ecuador.

**The acid technique** (a much more recently developed methodology) is a considerably more labor-intensive procedure also directly derived from yet another, even older commercial process.
a. The Solvent Extraction Technique (Scheme 1)

Macerate Leaf, Dust with Lime, Dampen with Water; Place into a Pozo Pit

↓

Add Kerosene and Mix Thoroughly; Let Sit

↓

Isolate Kerosene

↓

Add Fresh Dilute Sulfuric Acid to the Kerosene and Mix Thoroughly; Let Sit and Separate

↓

Isolate Dilute Sulfuric Acid Solution (Agua Rica)

↓

Add Base Until Alkaline (Coca Paste Precipitates)

↓

Filter and Dry

↓

Coca Paste

Direct Leaf-to-Base Option (See Scheme 3)
**b. Bazuco**

Chemically, the preparation of *bazuco* serves two purposes:

1. The diluent-slurred aqueous solution makes an excellent visual indicator of the interface boundary between the two layers; and

1. The first precipitate reportedly contains a relatively high content of the cinnamoylcocaines
c. The Acid Extraction Technique (Scheme 2)

1. Prepare Dilute Sulfuric Acid in a Pozo Pit
2. Add Dried Coca Leaf; Macerate via Stomping
3. Isolate Acidic Coca Juice; Filter into a Chiquero
4. Add Lime Slurry with Vigorous Stirring Until Alkaline
5. Add Kerosene and Mix Thoroughly; Let Sit and Separate
6. Isolate Kerosene
7. Add Fresh Dilute Sulfuric Acid to the Kerosene and Mix Thoroughly; Let Sit and Separate
8. Isolate Dilute Sulfuric Acid Solution (Agua Rica)
9. Add Base Until Alkaline (Coca Paste Precipitates)
10. Filter and Dry
11. Coca Paste

Direct Leaf-to-Base Option (See Scheme 3)
2. Coke Base (Scheme 3)

Dissolve Coca Paste into Fresh Dilute Sulfuric Acid (Reconstitutes Agua Rica Solution)

Direct Leaf-to-Base Option (from Schemes 1 and 2)

Add Concentrated Aqueous Potassium Permanganate and Mix Thoroughly; Let Sit (Manganese Dioxide Precipitates)

Filter Off Manganese Dioxide; Isolate Oxidized Agua Rica Solution

Add Dilute Ammonia Until Alkaline (Coke Base Precipitates)

Filter and Dry

Coke Base
3. Cocaine Hydrochloride (Scheme 4)

Dissolve Coke Base in Diethyl Ether; Filter (Constitutes Solution A)

↓

Dissolve Concentrated Hydrochloric Acid in Acetone (Constitutes Solution B)

↓

Add Solution A to Solution B; Mix Thoroughly and Let Sit (Cocaine Hydrochloride Precipitates)

↓

Filter and Dry

↓

Cocaine Hydrochloride
Illicit synthetic cocaine

1. Production of 2-carbomethoxytropinone;
2. Its conversion to Methyl Ecgonine; and
3. Benzoylation to Cocaine.
1,3-Acetonedicarboxylic Acid

HOAc

Acetonedicarboxylic Acid Anhydride

MeOH

2,5-Dimethoxytetrahydrofuran

H2SO4

NH2CH3

Acetonedicarboxylic Acid Monomethyl Ester

Succindialdehyde

(+,−)-2-Carbomethoxytropininone (2-CMT)

1.5% Amalgam H2SO4 pH 3.5–4.0 0–5 °C

(+,−)-Egonine Methyl Ester

Benzoyl Chloride

Pyridine

(+,−)-Cocaine

(+,−)-Pseudoecgonine Methyl Ester

Benzoyl Chloride
III. Licit (Pharmaceutical) Cocaine Production

Pharmaceutical cocaine is a by-product from the industrial extraction from coca of flavoring agents used in the soft-drink industry. The isolation process is proprietary and cannot be detailed in this study; however, it is known to proceed through numerous recrystallization and purification steps. The final product, cocaine hydrochloride, is generally of better than 99.5% purity.
IV. Forensic Differentiation of Licit Versus Illicit Cocaine

Illicit natural cocaine accounts for more than 99.99% of all seized exhibits. Exhibits of illicit synthetic cocaine are extremely rare. Pharmaceutical cocaine is rarely seen and is invariably the result of licit drug diversion or illegal prescriptions. The individual processes used to obtain each type of cocaine are distinct and give products that are chemically unique with respect to the presence and/or relative enhancement or diminution of various impurities. **Therefore, detailed forensic analysis can differentiate between all three types.**

A. Illicit Natural Cocaine  
B. Illicit Synthetic Cocaine  
C. Pharmaceutical Cocaine
Analysis illicit Coca products:
Macro- and Microscopical Examination:

_Erythroxylum coca_ leaves are green to brownish green in color, oval in shape and vary size and appearance from species to another.

Entire coca leaves are generally characterized by two lines parallel to the midrib on lower surface to form two raised ridges.

Powdered coca leaves is characterized by a papillae at lower epidermis with frequent prismatic of Ca oxalate and proserchymatous cells at the ridge region.
Lower epidermis in surface view showing papil-5 Calcium oxalate prisms (pap.) and paracytic stomata. 6 Collenchyma in transverse section. 2 Upper epidermis in surface view, with prisms of 7 Part of the lamina in sectional view showing the calcium oxalate (cr.) and underlying palisade upper epidermis, palisade and part of the(pal.). spongy mesophyll. 3 Part of the lamina in sectional view showing the 8 Epidermis from over a vein in surface view. Lower epidermis with papillae (pap.), stomata 9 Spongy mesophyll in surface view. And cells of the spongy mesophyll. 10 Lignified idioblasts and xylem vessels. 4 Fibres with part of a calcium oxalate prism 11 Lower epidermis in oblique surface view showing sheath, ing
For qualitative test (TLC, Colour Test)
Simple immersion in alcohol is sufficient for extraction of alkaloids.

**Colour Test:**

**Cobalt thiyocyanate Test:** put suspected material in test tube T.T.+one drop of 16% aquous HCl+one drop of cobalt thiyocyanate \([\text{Co(CN}_2\text{)}_2]\) SHAKE FOR 10 SECONDS THEN ADD ONE DROP OF REAGENT AGAIN SHAKE BLUE COLOR INDICATED THE POSSIBLE PRESENCE OF COCAINE.
Wagner Test (I$_2$/ KI)

Small amount of suspected material in T.T.+ few drops of H2O shake for few seconds +2 drops of reagent give brown ppt indicate cocaine base does not give this precipitate.
Microcrystal Test:

5% aqueous paltinic chloride
2mg of sample + one drop of HCl (1N)+ one drop of 5% aqueous paltinic chloride examine under microscope after 10 minutes Delicate Feathery crystals are slowly developed become heavier in structure by time.
Chromatographic analysis: (TLC, GLC and HPLC)
GLC and HPLC are used for quantitative estimation of cocaine

**TLC:** Simple methanolic solution is used for spotting system
- **CHCl₃: Dioxane: EtOAc: Diethylamine** (25:60:10:5)
- **Cyclohexane: Toluene: Diethylamine** (75:15:10)

**Revelators:** Dragendorff’s reagent or freshly prepared acidified potassium iodopaltinate reagent. 1st reagent give orange color while second give blue color.
**GLC:** Ov-1 or SE-10 packed or capillary column
The analysis is carried out on the silylated derivatives. Quantitation can be determined by peak area and concentration response curve.

**HPLC** using Rp-18 column with MeOH:H2O: 1%H3PO4:n hexylamine (300:700:1000:
Standard solution: 1 mg of each cocaine, cis and trans-cinnamoyl cocaine, procaine, lignocaine, amylocaine, butacaine and bezocaine are dissolved in 10 ml mobile phase.
Detection: UV lamb at 230 nm
Quantitation: by peak area, internal or external standard.
Spectroscopic Analysis: IR spectroscopy allows accurate and precise method for identification of cocaine HCl, cis and trans cinnamoyl cocaine isomers
Metabolism and excretion:

Two major metabolites, benzoylecggonine and ecgonine methyl ester through demethylation and debenzoylation process respectively. Some other minor metabolites including norcocaine.
In acute users (single dose)

- Cocaine can be detected for up to 24 hours and its metabolites for up to 48 hours. After chronic use, detection time attaining up to 5 days or more.

- The detection of cocaine and its metabolites in a urine sample is considered as a prove for previous cocaine consumption.

- The peak plasma level of cocaine is reached shortly after intranasal, intrapulmonary or intravenous administration the time of maximum psychotropic and physiological effects is also short, therefore the euphoric effects diminish within 30-60 minutes.
Analysis of cocaine and its metabolites in the urine:

-Cocaine and its metabolites (ester) show poor stability especially in alkaline media. Urine sample should be kept cool and in the dark as much as possible after collection.

- Extraction of cocaine from urine should be done under dry condition using Na2SO4. SPE is also used using diatomaceous earth or RP-18 cartliage.
Initial Screening Methods:

1) **Immunoassay Method:** antibodies of the commercial immunoassay kit are targeted towards Benzoylcgonine. The detection limit of the assay is 300 ng/ml

2) **TLC:** similar to qualitative test but here standard solution used are cocaine, benzoylcgonine and ecgonine methyl ester. TLC is visualized either by UV at 254 or spray reagent. The detection limit of HPTLC for cocaine and benzoylcgonine is 0.3 mg/liter urine while conventional TLC has detection limit about 1 mg/liter urine.
Confirmatory chromatographic methods:

**GLC:** it is carried out on acylated or silylated derivatives of the urine extract.  
**GC-MS:** a mass spectrometer is used as a detector in connection with GC machine.

**El mass spectral data for cocaine and its metabolites:**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Principle</th>
<th>fragment</th>
<th>ions (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>underivatized</td>
<td>Acyll alkyl derivatives</td>
<td>Trimethylsilyl derivatives</td>
</tr>
<tr>
<td>Cocaine</td>
<td>82,182, 303, 105</td>
<td>Not formed</td>
<td>Not formed</td>
</tr>
<tr>
<td>Benzoylecgonine</td>
<td>124,168,82,93</td>
<td>300, 421,316,272</td>
<td>82,240,361</td>
</tr>
<tr>
<td>Ecgonine methyl ester</td>
<td>82,96,168,199</td>
<td>182,345,119</td>
<td>82,96,83,98,186</td>
</tr>
</tbody>
</table>

**HPLC:** The use of HPLC with Rp-18 column and UV detector provides a sensitive method for detection of cocaine and its metabolites.
Summary

the detection of cocaine and its metabolites in a urine sample is the best indication of previous consumption of cocaine and cocaine-containing products.