Psychomotor Stimulants

- Historical Perspective: Amphetamine
  - synthesized in the 1920s
  - replaced naturally occurring sympathomimetic ephedrine
  - several therapeutic uses
- 1932: Benzedrine (brand name) inhaler was introduced
  - potent dilator of the bronchial tube

Historical Perspective, cont.

- 1935: Effective treatment for narcolepsy
  - would awaken anesthetized dogs
  - today also use methylphenidate (Ritalin)
- 1937
  - available as a prescription tablet
  - reduced activity in hyperactive children
  - methylphenidate: suppression of growth
  - amphetamine ideal for cramming

Historical Perspective, cont.

- 1938: Paranoid psychotic reactions documented in patients with narcolepsy
- 1939
  - appetite-suppressant effects
  - effect is small and limited in duration
  - 4 to 6 weeks later tolerance occurs
  - German soldiers used to increase their efficiency
  - widely used in Japan during World War II

Historical Perspective, cont.

- 1950s and early 60s: Prescribed for depression and feelings of fatigue
  - problem: mood falls below predrug levels
  - amphetamine is contraindicated
- 1970s
  - restricted legal use to 3 conditions
  - narcolepsy, ADHD, short-term weight loss
  - restrictions on prescriptions and refills
  - public opinion shifted

Amphetamine

- Phenethylamine nucleus
- Isomers of amphetamine
  - d- and l-amphetamine
  - Benzedrine: equal mixture of both forms
  - methamphetamine also known as crank
- Other forms
  - ephedrine
  - ice: smokable form of methamphetamine hydrochloride crystals

Amphetamine

- d-amphetamine
  - 3 to 4 times more potent than l isomer
  - first marketed as Dexedrine
- Methamphetamine (Methedrine)
  - contains a methyl group & crosses BBB more readily
  - sympathomimetic effects: slightly more active than d isomer
  - once used to stimulate respiration following barbiturate overdose in ERs
Amphetamine

- Pharmacokinetics
  - oral administration
    - peak effects occur 2 to 3 hrs after ingestion
    - half-life is 10 to 12 hours
    - stable plasma levels can be maintained by oral administration using 4 to 6 hr intervals
    - virtually complete elimination occurs within 2 days after the last dose
  - intravenous administration
    - onset to peak effects occur more rapidly
    - tachyphylaxis

Psychomotor stimulants

- Historical Perspective: Cocaine
  - derived from Erthroxylan coca (coca plant)
    - evergreen
    - principal habit: South America
    - desired height of 3 to 6 feet
    - leaves are elliptical in shape
    - leaves with greatest cocaine alkaloid concentrations are rejected for coca chewing

Historical Perspective, cont.

- 11th Century: The Incan civilization
  - inception of coca use: 6th century AD
  - plant an integral part of Incan civilization
  - Incan myths
    - coca grew from the remains of a woman cut in half and was only to be consumed by men
    - coca plant was created by the God Inti and Mama Quilla cultivated the plant in humid valleys

Historical Perspective, cont.

- The 1500s: Advent of Spanish colonialists
  - initially unpopular: European explorers returning from Peru brought back supplies of coca leaves
  - Spanish colonialists initially tried to eradicate coca use
  - plants stimulating properties: proclaimed coca essential to the well-being of Andean Indians

Historical Perspective, cont.

- The Late 1800s: Increased popularity
  - isolation and extraction of cocaine
    - Gardeke (1855): extracted the active constituent called erythroxylon
    - Niemann (1860): isolated the alkaloid and chemically characterized it and named it cocaine
  - development of the hypodermic syringe

Historical Perspective, cont.

- The Late 1800s: Early therapeutic uses
  - Dr. Paul Mantegazza: subjective effects
  - Freud (1884): planned to use it as a therapeutic agent (heart disease, nervous exhaustion, morphine addiction)
  - Ernst Von Fleischl-Marxow: first cocaine addict in Europe
  - Karl Koller: local anesthetic properties of cocaine
Historical Perspective, cont.
- The Late 1800s: The Patent Medicine Era
  - cocaine-containing products
    - nose powders
    - suppositories
    - throat lozenges and sprays
    - wine, soft drinks
    - cigarettes
  - cure maladies (e.g., alcoholism, opiate addiction, venereal disease, colds, corns)

Historical Perspective, cont.
- Vin Mariani
  - popular brain tonic developed by Angelo Mariani
  - 2 ounces of coca leaves soaked in 18 ounces of red wine with an added garnish of cocaine (100 mg/glass)
  - received written endorsements from over 7,000 eminent physicians
  - Pope Leo XIII, H.G. Wells, Edison vouched for its uses

Historical Perspective, cont.
- Coca-Cola (1886)
  - offered the beneficial effects of coca without the deleterious effects of alcohol
  - intellectual beverage and temperance drink that cured all nervous afflictions
  - 1903: Coca-Cola admits cocaine is present in their soft drink, shortly thereafter they elected to quietly remove it
  - 1906: government analysis reveals cocaine is no longer present

Historical Perspective, cont.
- End of Patent Medicine Era
  - deleterious effects of cocaine and opium lead to strict legal restrictions
  - 1910: President William Taft advises congress that cocaine poses the most serious drug problem
  - 1914: President Woodrow Wilson signs the Harrison Narcotics Act of 1914

Cocaine
- General pharmacology
  - hydrophilic and hydrophobic domain
  - rapidly penetrates into brain tissue
  - sequestered into fat tissue
  - increases cocaine's potency
  - prolongs its short duration of action
  - increases its potential toxicity

Cocaine
- Pharmacokinetic profile
  - rapid onset and short duration of action
  - elimination half-life is approximately 50 minutes
  - elimination half-life is as short as 19 min following IV administration
  - primary metabolites include: norcocaine, benzylecgonine, and benzoylnorecgonine
  - small amount of cocaine is usually excreted unchanged via the urine
### Cocaine

- **Common forms of cocaine**
  - cocaine hydrochloride
  - freebase cocaine
  - crack cocaine
  - coca paste

### Forms of Cocaine

- **Cocaine hydrochloride**
  - salt form of cocaine
  - commonly used for sniffing or injection
  - water soluble & chemically stable
  - series of extraction processes that require volatile organic solvents
    - extract total base from leaf material with a solvent

- **Freebase cocaine**
  - smokable form of cocaine
  - separate cocaine base from the salt form
  - cocaine base vaporizes at 90°C
  - average temperature for tobacco burning (400-600°C) only 6% of the drug survives pyrolysis
  - users smoking from a glass pipe will consume less than 50% of the drug

- **Crack**
  - simple, inexpensive way to manufacture freebase cocaine
  - offers a safer alternative to traditional freebasing
    - no organic solvents around heat
    - viable alternative for those afraid of needles or of contracting the AIDS virus
    - less time consuming

### Forms of Cocaine

- **Cocaine hydrochloride**
  - extraction process, cont.
    - alkaloids are put into an aqueous acid solution followed by solvent extraction to remove any nonalkaloid impurities
    - acid solution is then neutralized so that the partially purified cocaine base may be extracted and isolated
    - a re-crystallization process yields a powder of fine white flakes that can have a purity of 90 to 100%

- **Freebase cocaine**
  - production of freebase cocaine
    - dissolve cocaine hydrochloride in water and add a strong base (e.g., ammonium hydroxide)
    - volatile organic solvent (e.g., petroleum ether) is then added to extract the alkaloid
    - crystallization of the freebase
    - cocaine base can then be heated and smoked in a pipe

- **Crack**
  - simple, inexpensive way to manufacture freebase cocaine
  - offers a safer alternative to traditional freebasing
    - no organic solvents around heat
    - viable alternative for those afraid of needles or of contracting the AIDS virus
    - less time consuming
**Forms of Cocaine**

- **Crack**
  - made by mixing cocaine hydrochloride with baking soda and water
  - can be smoked or injected
    - pieces of crack called “rocks” are heated and inhaled by the user
    - users dissolve cocaine rocks with an acid (e.g., vinegar, Kool Aid, lemon juice) and inject it
      - aversive effects: hallucinations, heart fluttering
      - burning sensation
      - report a more intense rush

- **Coca paste**
  - popular in South America
  - mixed with tobacco and smoked
  - coca paste is made by:
    - thoroughly soaking coca leaves in an organic solvent (e.g., gasoline or kerosene)
    - leaves are then mixed and mashed and excess fluid is filtered out leaving residual coca paste
  - ranges from 30 to 90% freebase cocaine

**Routes of Administration**

- **Oral administration**
  - chewing of coca leaves
  - least desirable route of drug administration
    - slowest rate of drug delivery to the brain
    - small percentage of the drug is distributed to the brain via the circulatory system
      - stomach enzymes
      - high stomach acidity
      - hepatic metabolism
      - incomplete intestinal absorption
    - euphoric effects are greatly diminished

- **Intranasal administration**
  - cocaine is absorbed through the nasal mucosal membranes
  - user usually “snorts” a line containing 20 to 30 mg cocaine hydrochloride
    - stimulatory effects: last 20 to 40 min
    - there is no “rush”
  - adverse health consequences include:
    - perforated nasal septum
    - chronic rhinitis

**Intravenous administration**

- cocaine is injected directly into a vein
- use cocaine hydrochloride or dissolved crack rocks
- very efficient route of drug delivery
  - first passes through the lungs
  - approx. 25% passes through liver before being distributed by the circulatory system
  - a small amount is lost through exhalation and hepatic metabolism
Routes of Administration

- Intravenous administration
  - slower than pulmonary absorption
  - produces an intense “rush” within 1 to 2 minutes following an injection
  - peak brain, tissue, and plasma concentrations are reached within 15 min following an IV cocaine injection
  - adverse health consequences include:
    - veins collapsing
    - AIDS

- Intravenous administration
  - inject directly into the arterial supply
  - most efficient route: assures virtually 100% drug delivery to the brain capillaries
  - no first-pass elimination or pulmonary excretion
  - only limiting factor is drug diffusion through the capillary walls to brain tissue
  - high fatality rate

- Intravenous administration
  - smoking of freebase or crack cocaine
  - second most efficient route of drug administration
  - cocaine is rapidly delivered to brain tissue
  - produces an intense euphoric “rush”
  - users rate subjective effects higher than IV
  - users may have a craving to repeat their drug use within 10 to 30 min

DSM Diagnostic Criteria

- 1952: American Psychiatric Association published the first Diagnostic and Statistical Manual (DSM-I)
  - manual classifies mental disorders
  - lists the essential criteria for a diagnosis
  - Uses more neutral terms
  - substance abuse & substance dependence
  - Has undergone many revisions
  - Currently using DSM-IVR

- Substance Use Disorder section
  - outlines essential features of dependence
    - all of the criteria do not have to be present
    - some criteria are more prevalent in one substance dependency than in another
    - addiction is viewed as a specific instance of psychopathology
    - represents a qualitative measure

- Substance Use Disorder section
  - devised primarily by observing conditions following chronic alcohol and opiate use
    - discontinued alcohol and opiate use create strong physical dependence
    - easily discernable withdrawal signs
    - reliably exhibited across users
DSM Diagnostic Criteria

Prior to DSM-III (1987) cocaine dependence was not even recognized
- tolerance and withdrawal were considered essential features
- investigators felt cocaine did not produce either tolerance or withdrawal

Bozarth & Wise (1985): Rats given unlimited access to cocaine displayed a 90% mortality rate within 30 days

DSM Diagnostic Criteria

Substance Use Disorder section
- present criteria
  - tolerance and withdrawal are no longer essential for the diagnosis of substance dependence
  - recognizes that cocaine withdrawal is more subtle than alcohol and opiate withdrawal
- changes incorporated over the years reflect the evolution of the APA’s concept of addiction

Cocaine Addiction

Use patterns
- episodic drug use
  - drug use: usually separated by 2 or more days
  - binges: bouts of drug-taking behavior
  - common misconception: safer than daily use
- daily or almost daily drug use
  - less frequently displayed by cocaine users
  - use cocaine throughout the course of day or restrict use to only certain hours within a day
  - generally increase their cocaine dose over time

Cocaine Addiction: The Bingeing and Crash Cycle

General description of a binge cycle
- episodic drug use alternates with periods of drug abstinence
- typical user can consume several grams of cocaine during a single binge
- typically lasts about 12 hours to several days
- drug users may administer cocaine as frequently as every 10 to 15 min

Cocaine Addiction: The Bingeing and Crash Cycle

Cocaine withdrawal
- withdrawal phase follows “crash” phase
- no grossly observable withdrawal signs
  - anergie
  - anhedonia
- withdrawal signs are inversely related to cocaine’s stimulatory effect
- withdrawal signs are weakest immediately following the “crash” phase and increase in intensity over the next 12 to 96 hrs
Cocaine Addiction: The Bingeing and Crash Cycle

- Cocaine craving
  - intense craving can be elicited by environmental stimuli
  - during drug abstinence users may feel dysphoric and recall memories of the drug-induced euphoria
  - recalled memories may further intensify drug craving
  - craving may be responsible for drug relapse

Cocaine Euphoria
- present with all routes of administration
- desire to intensify the “rush” leads to a more rapid route of administration
- “euphoric rush”
  - produced by IV and inhalation administration
  - lasts only a few minutes
  - user describes as orgasmic
  - may be produced by cocaine’s rapid entry into the brain

Limitations of the DSM Diagnostic Criteria
- Fails to adequately describe conditions that surround drug-taking behavior
- Stimulants do not produce physical dependence
- Stimulant withdrawal signs
  - more subtle than classic withdrawal signs
  - show more individual variation
- Stimulants produce sensitization

Alternative to the DSM Diagnostic Criteria
- Drug addiction can be viewed as a motivated behavior that progresses along a continuum
- Emphasize the extreme control a drug exerts over an individual’s behavior
  - motivational strength
  - motivational toxicity

Parallel Indices in Humans
- Motivational strength
  - high drug acquisition costs
  - risk-taking behavior
- Motivational toxicity
  - poor nutrition status
  - loss of libido

Parallel Indices in Pre-clinical Studies
- Motivational strength
  - progressive ratio testing
  - the amount of aversive stimuli tolerated
- Motivational toxicity
  - examine self-administration behavior using unlimited access testing
  - use forced-choice testing under conditions of deprivation
Chemically Related Compounds

[Chemical structures]

Early Advertisement for Medicinal Cocaine

Advertisement for Vin Mariani

[Image of an advertisement for Vin Mariani]