

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 *Erythroxylon 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, benzoylecgonine, and benzoynorecgonine
- 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

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%

Forms of Cocaine

- 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

Forms of Cocaine

- Freebase cocaine
 - produces an intense euphoric rush
 - extraction process is time consuming and dangerous
 - 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

Forms of Cocaine

- 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

Forms of Cocaine

- Crack
 - origin of the term “crack”
 - “small rocks” were cracked off of larger pieces before being sold
 - crackling sound that is made when crack is smoked in a pipe
 - largely responsible for the “second epidemic” of cocaine use that occurred in the 1980s

Forms of Cocaine

- 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

Routes of Administration

- 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

Routes of Administration

- 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

Routes of Administration

- Intra-Arterial 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

Routes of Administration

- Pulmonary 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

DSM Diagnostic Criteria

- 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

DSM Diagnostic Criteria

- 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

- General description of a binge cycle
 - users terminate a binge
 - collapse from physical exhaustion
 - deplete their drug supply
 - “crash” phase follows a binge
 - users suffer from extreme exhaustion & fatigue
 - usually sleep 12 to 14 hrs sometimes longer
 - hyperphagia alternates with sleep periods
 - initial phase of the crash: may show signs of intense depression, agitation, and anxiety

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 Addiction: The Bingeing and Crash Cycle

- 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

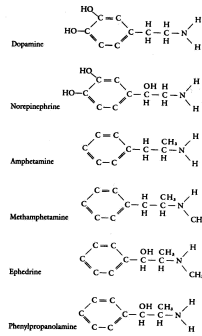
Parallel Indices in Humans

- 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



Early Advertisement for Medicinal Cocaine



Advertisement for Vin Mariani

New Life, New Vigor
 Experienced by all who have had occasion to use

VIN MARIANI

This Popular French Tonic-Stimulant is Invariably Agreeable and Efficacious,
STRENGTHENS, REFRESHES, RESTORES THE VITAL FORCES

When overworked, and for body or mental fatigue, nothing equals "VIN MARIANI" for immediate and lasting beneficial effect.
 This assertion is based on

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 from over 7,000 eminent Physicians and continued use over 30 years, in Hospitals, Public and Religious Institutions everywhere.

AT DRUGGISTS AND GROCERS.
 For Illustrated Book with Portraits and Autographs of Celebrities, address:
 Mariani & Co., New York.