

# STREET DRUG PHARMACOLOGY

## PART I: INTRODUCTION

Drugs are substances other than food or water introduced into the body for the purpose of producing physical or psychological change. Not all drugs, however, produce intoxicating effects. For example, birth control pills and antibiotics do not produce a “high.” Drugs that have an intoxicating effect are known as **psychoactive** substances. These drugs have the ability to *directly* affect mood, thinking or behavior.

The majority of psychoactive drugs are **controlled substances**. These substances are subject to the The Controlled Substances Act (**CSA**), which was enacted into law by Congress as Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970. The CSA is the legal basis by which the manufacture, importation, possession, and distribution of certain drugs are regulated by the federal government of the United States. The CSA created five Schedules (classifications), with varying qualifications for a drug to be included in each. Two federal departments, the Department of Justice and the Department of Health and Human Services (which includes the Food and Drug Administration) determine which drugs are added or removed from the various schedules. Classification decisions are required to be made on the criteria of:

- 1) Potential for abuse
- 2) Accepted medical use in the United States
- 3) Potential for addiction

Schedule I substances have no accepted medical value in the U.S., and a high potential for abuse and dependency. Schedule II drugs have accepted medical value in the U.S., but also a high potential for abuse and dependency/addiction. Drugs in schedules III-IV have increasingly lower potential for abuse and dependency/addiction.

Some schedule I drugs:

- Heroin
- LSD
- PCP
- Marijuana
- MDMA (“ecstasy”)

Some Schedule II drugs:

- Cocaine
- Oxycodone (OxyContin®, Percodan®)
- Methadone
- Amphetamines (including methamphetamine)
- Short-acting barbiturates (e.g., secobarbital/Seconal, pentobarbital/Nembutal)

Some Schedule III drugs:

- Hydrocodone (Vicodin®)
- Ketamine (“special K”)
- Testosterone

Some Schedule IV drugs:

- Most benzodiazepines (e.g., Xanax, Librium, Klonopin, Valium)
- Long-acting barbiturates (Phenobarbital)
- Zolpidem (Ambien®)

Some Schedule V drugs:

- Cough medicines containing codeine

State governments can place tighter controls on drugs that are mentioned in the CSA, but can not make the penalties for possession, manufacture and/or sales less serious. In Illinois, certain drugs (e.g., methamphetamine, short-acting barbiturates and some prescription opiates) are known as **designated products**. In order to prescribe any of these drugs, a physician or dentist must complete a special triplicate prescription form. One copy stays with the prescribing doctor, one goes to the pharmacy, and one goes to the Division of Alcoholism and Substance Abuse (**DASA**) within the Illinois Department of Human Services. DASA is charged with monitoring the prescribing practices of health care professionals as well as identifying and following up any unusual prescribing patterns. For example, it would not be normal for a dermatologist (skin specialist) to prescribe large quantities of pain-killing drugs. On the other hand, it is predictable that oncologists (cancer specialists) would have a relatively high rate of prescribing these drugs since pain is a frequent symptom of cancer.

### **Drug Names**

One of the things you may have noticed in the list of controlled substances is that drugs have different types of names. These are:

- **Chemical name:** This name indicates the chemical structure of the drug, and how the molecules of the drug are arranged. For example, Valium’s chemical name is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. Few drug users know the chemical names of the drugs they take, and virtually none of them use it.
- **Generic name:** Also known as the international nonproprietary name. This is the official name given to a pharmaceutical substance, as designated by the World Health Organization (WHO). Valium has the generic name *diazepam*.
- **Brand name:** The name given to a drug by a specific company. This name is protected by a patent, and can be used only by the company holding the patent.
- **Street or slang name:** An informal drug name that usually describes:
  1. What the drug looks like (crystal [methamphetamine], snow [cocaine], Humbolt County Green [marijuana], windowpane [LSD]),
  2. The alleged source (Maui Zowie [marijuana], B.C. buds [marijuana])

3. The drugs action (smack [heroin], downers [tranquilizers and hypnotics/sleeping pills])
4. Some other characteristic (ex: sinsemilla- actually sin semilla, Spanish for "without [sin] seed [semilla]").

Valium does not have a commonly-used slang name.

These names vary from State to State, city to city, and even neighborhood to neighborhood. A street name in one part of the country may refer to a completely different drug than it does in another part. The purpose of the slang name is to avoid detection by police, family members or other people, and/or to strengthen the culture of addiction.

### **Drug Measurement**

Drugs also vary in how they are measured. English measurement is used to weigh some drugs. Examples would be pounds (large quantities of marijuana, cocaine, heroin or methamphetamine) or ounces (marijuana or large amounts of cocaine, heroin or methamphetamine). Many drugs are measured using metric units. The basic metric weight is a gram (gm), which is approximately  $1/28^{\text{th}}$  of an ounce. Anytime a metric measure is preceded by "kilo" it means 1000x the measure, so a kilogram (kg) is 1000 grams. "Milli" means  $1/1000^{\text{th}}$  of whatever is being measured, so a milligram (mg) is  $1/1000^{\text{th}}$  of a gram, or  $1/28,000$  of an ounce. "Micro" is  $1/1,000,000^{\text{th}}$  of whatever is being measured, so a microgram (mcg) is  $1/1,000,000^{\text{th}}$  of a gram or  $1/28,000,000$  of an ounce. While many drugs are measured in grams and milligrams, only one substance is powerful enough to be measured in micrograms: LSD.

Many drugs are measured using street terms, such as:

- Nickel/nickel bag & dime/dime bag = \$5 or \$10 worth of drug
- Eight ball =  $1/8$  oz. (3.75 grams)
- Sixteenth = either  $1/16$  oz (1.875 gm) or  $1/16$  gm (62.5 mg, about three lines of cocaine)
- Line = an elongated pattern of powdered drug. Quantity = whatever the user decides.
- Joint = a marijuana cigarette.
- Joy stick/happy stick/dip/sherm/wicki stick = one joint or cigarette treated w/PCP.
- Hit = 1) one dose (a "hit" of acid/LSD); 2) a puff on a pipe or joint.
- Older terms: lid (an ounce of marijuana), piece (an ounce), spoon ( $1/16$  oz.).

### **Drug Forms**

Psychoactive drugs come in many different forms, including plant/botanical matter (marijuana, opium poppies, khat, coca, peyote, psilocybin mushrooms, jimson weed), liquids (alcohol, pure LSD, injectable pharmaceuticals), powders (cocaine hcl. [cocaine powder], heroin, PCP, and methamphetamine), pills (tablets, capsules, caplets of either pharmaceutical or illicit origin) and other forms (e.g., "rocks" of "crack" cocaine or methamphetamine/"ice").

### **Potency, Purity and Misrepresentation**

Potency refers to the strength of the drug, compared to some other drug of a similar type. For example, it takes about 120 mg of codeine to equal the analgesic (pain-killing) ability of 10 mg of morphine or 4 mg of heroin. Morphine is 12x more potent than codeine, while heroin is 2.5x more potent than morphine and 30x more potent than codeine.

Purity is the major determinant of potency. The more pure the drug, the potent it is. Street drugs are seldom pure, but are commonly misrepresented in one of three ways:

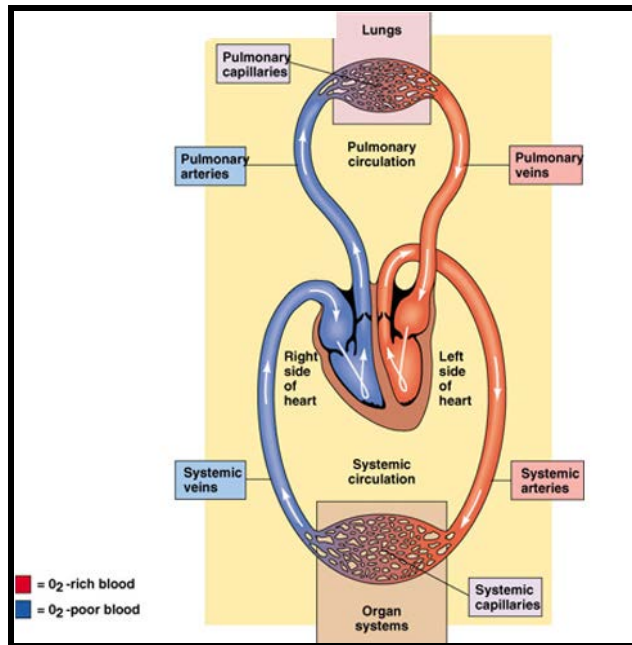
- **Adulteration:** (to adulterate = to "step on"/"hit"/"dance on" "cut" a drug). The alleged drug may be adulterated with an additional drug, or with other active substances (which produce their own physical/psychological effect) or inactive substances (ex: cornstarch, mannitol) which have little or no effect of their own on physical/psychological functioning.
- **Substitution-1:** None of the alleged drug is present, but another drug/drugs is/are. For example, the vast majority of the time, alleged THC is actually PCP, occasionally mixed w/ other drugs.
- **Substitution-2:** None of the alleged drug is present, and neither is any other drug or active substance. An example would be catnip or oregano sold as marijuana or an inactive (lacking psychoactive effects) powder sold as cocaine, heroin or methamphetamine.

### Methods of Administering Drugs

It is important to understand how the methods of administering a drug changes the effect, and the time factors connected to each method of administration. The ultimate goal of administering or taking a psychoactive drug is to send the substance to the brain via the bloodstream. Three important questions are:

- How does the drug enter the bloodstream, (**method of administration**)
- How long does it take for the drug to take effect (**onset of action**)
- How long the effect of the drug lasts (**duration of action**).

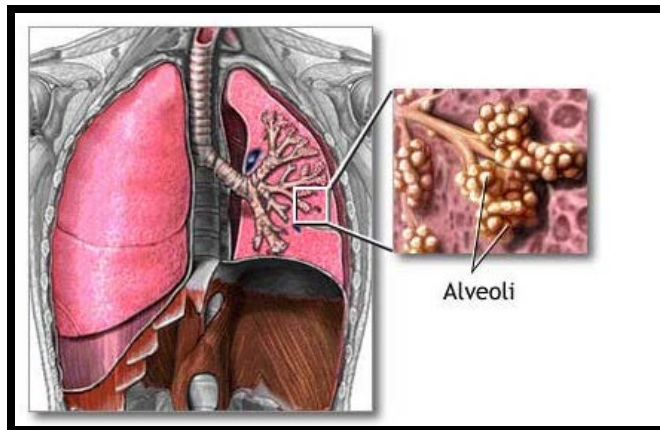
First, we need to examine **the route of circulation**. Blood flows in a circle according to this pattern: capillaries, veins, vena cava (the large vein entering the heart), right side of the heart, lungs, left side of the heart, aorta (the large artery which carries blood out of the heart to the body), capillaries, etc. The following illustration shows the route of circulation.



- Ingestion:** This refers to oral administration (swallowing). The drug usually needs to dissolve in the stomach before entering the bloodstream from the digestive system. Onset is relatively slow, and duration relatively long. This because the substance needs to be broken down into particles that can pass through the walls of the stomach, enter the bloodstream and follow the full route of circulation. The drug can sometimes be removed from the body before producing its full effect either by gastric lavage ("pumping the stomach"), emesis (inducement of vomiting), and/or absorption (the use of activated charcoal ["the universal antidote"]).
- Insufflation ("snorting").** Certain drugs (e.g., cocaine, heroin, PCP) can be sniffed into the nose and absorbed through a mucous membrane (soft, moist tissue) into the capillaries (tiny blood vessels). Some areas that have abundant mucous membrane tissue are the inside of the mouth, throat, vagina and anus. When drugs are snorted, the onset is normally faster than ingestion and duration is normally in the medium range, because the drug is already in a form that can be immediately absorbed into the bloodstream. It is difficult if not impossible to remove the drug from the system once it has been taken.
- Injection ("shooting"/"firing"/"slamming"/"mainlining").** Although most drugs can be injected **subcutaneously** (under the surface of the skin/"**skin popping**") or **intramuscularly (i.m.)**, most injectors use the **intravenous (i.v.)** route, injecting directly into a vein. This method can produce an onset of action in 10-15 seconds because the drug does not have to pass through capillaries before reaching a vein. Duration of action is normally brief when compared to ingestion or snorting. This is no viable way of removing the drug from the system once it has been injected.



- **Smoking.** This method of drug use produces an onset in as little as 7-10 seconds, and is associated with a brief duration of effect, about the same duration as shooting. The rapid onset occurs because the drug enters the bloodstream through the lungs, and so skips the entire right side of the heart. Although the user can remove some of the drug from his/her system by coughing, most of the substance is absorbed into capillaries through the lungs' **alveoli (air sacs)** immediately. An important question when discussing smoking is how long it takes to inhale a full dose of the drug in question. A full dose of “crack” can be inhaled in one breath, while an effective dose of marijuana can usually not be inhaled in less than three or more breaths, often more. Naturally, the number of inhalations needed to produce a marijuana high depends on the potency of the drug, with very high potency marijuana capable of producing a high in 1-2 breaths.



Another important concept related to the method of administration is the "**rush**" or "**flash**". When drugs are injected intravenously or smoked, the virtually immediate onset (the rush) is the most pleasurable part of the experience. It is the "icing", and the rest of the drug experience, whether it is 10 minutes or hours in duration, is the "cake". A rush may occur when drugs are snorted or ingested, but the intensity is less because of slow onset of action (measured in minutes rather than seconds).

### **Metabolism and Excretion**

After a drug produces its effect, it is broken down or **metabolized**. The amount of time this takes can vary depending on the drug as well as on the physical condition of the

user. After drug-related liver damage, for example, it may be difficult for that organ to metabolize psychoactive substances.

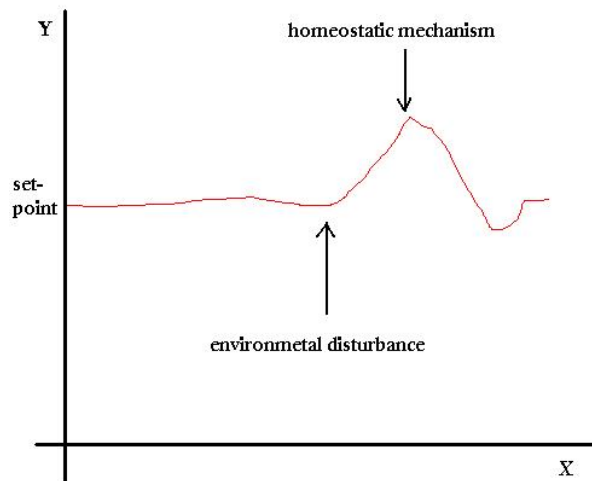
Once drugs are metabolized, they are **excreted** (removed from the body). **Excretion** can occur in urine, feces, perspiration or in the breath, depending on the drug. Most drugs leave the body, either partially or completely, in urine. This makes urine testing the most common method of detecting drug use. Urine tests can detect drugs for days, weeks or months, depending on the particular drug and the length and intensity of use. In many cases, what is detected in urine is not the drug itself, but one of its **metabolites** (breakdown products). For example, heroin shows up in the urine as morphine in urine, and cocaine as the metabolite benzoylecgonine.

## **Mechanisms of Tolerance**

### **Homeostasis.**

The human body needs to keep its functions (pulse rate, body temperature, blood pressure, etc.) within certain limits. For example, internal body temperature is normally 98.6° F., give or take a degree or so. This normal internal body temperature will be called the “set-point.” When one’s temperature gets too high, one perspires in order to give off heat; if it gets too low, one shivers in order to produce heat. This tendency to maintain a stable physical condition is called homeostasis (homeo = same/stasis = state). The need to maintain homeostasis is the primary reason for the development of tolerance.

In the following illustration, the set-point could be the breathing or pulse rate, body temperature, or any other physical function. The “environmental disturbance” represents the drug in question. As you can see, when a drug changes the set-point of any physical function, a “homeostatic mechanism” brings the function back into the normal range. As described below, the homeostatic mechanism could be the production of liver enzymes, an increase or decrease in the activity of the nervous system, or some other protective procedure.



**Tolerance:** refers to the drug user's need over time to increase the dosage of the drug in order to achieve the desired effect. It can also be said that tolerance exists when the dosage of the drug that the user is accustomed to no longer is sufficient to produce the desired effect. There are two types of physiological tolerance and one that is psychological in origin:

- **Metabolic/enzyme induction tolerance.** One of the liver's most important jobs is to produce **enzymes** (chemicals which change other chemicals but are not changed themselves). Some of these enzymes are involved in metabolizing psychoactive substances, and these enzymes will increase in amount when psychoactive drugs enter the body. The increase in enzymes produces tolerance, which results in the drug user increasing the dose, which results in more enzyme production, which results in higher tolerance, which causes the user to increase the dose even more, and so on. An increase in liver enzymes is one sign that can help a physician diagnose chemical dependency. For example, high levels of the liver enzymes **SGOT** and **SGPT** are often found in alcoholics.
- **Pharmacodynamic tolerance.** When psychoactive drugs cause bodily functions to exceed or go below their normal range, the **central nervous system** (CNS/the human brain and spinal cord) begins to “reset” itself. An example of this would be that when heroin or Valium use causes the breathing rate to fall too far, the CNS will increase its activity in order to push the breathing rate up into the normal range. This produces an increase in tolerance as well, and the drug user now requires a larger dose to “get high”. The higher dose results in even greater CNS activity, and so on.
- **Behavioral tolerance.** This type of tolerance is psychological in origin, and at least partially voluntary. It occurs when a “high”/intoxicated person is confronted with the need to appear normal, and therefore begins to act less intoxicated. For example, a person who is overly sedated may make a greater effort to speak clearly and walk

without swaying in the presence of spouse, parent, police officer, etc. Behavioral tolerance can't overcome all drug effects, but it is effective on some.

### **Addiction/physical dependency/withdrawal**

**Addiction:** The term “addiction” usually refers to **substance dependency** (DSM-IV-TR<sup>1</sup>). **Substance abuse** is a different disorder which is often, but not always, less severe than substance dependency. Substance dependency can be described less formally than it is in the DSM through five different criteria:

**Compulsion:** Inability to rationally decide when and where to begin a drinking/drugging episode).

**Loss of control/inability to use with intent:** Once a drinking/drugging episode has started, there may be loss of control over how much is consumed, how long the episode lasts, or what will happen as a result of the drinking/drugging: ("I'll just have one beer, then go home"/"When it gets to be midnight, I'll stop tooting coke and go to sleep").

**Continued use despite adverse/negative consequences:** When some behavior begins to cause physical, psychological or spiritual consequences, the person who is engaging in that behavior usually stops or cuts down. Continuing to drink or drug despite the negative consequences of that behavior is irrational.

**Tolerance:** Drug tolerance is a possible but not required criterion for substance dependence.

**Physical dependence/withdrawal.** Physical dependence is defined by the appearance of withdrawal symptoms upon abrupt discontinuation of drug use. This is a possible but not required criterion for substance dependence. Physical dependence and associated withdrawal symptoms are a side effect connected to the use of abused substances which are sedating in nature, such as opiates, barbiturates and benzodiazepines.

**The severity of withdrawal symptoms** varies from potentially life-threatening (barbiturates and certain other hypnotics) to moderate to severe physical discomfort without threat of death (opiates).

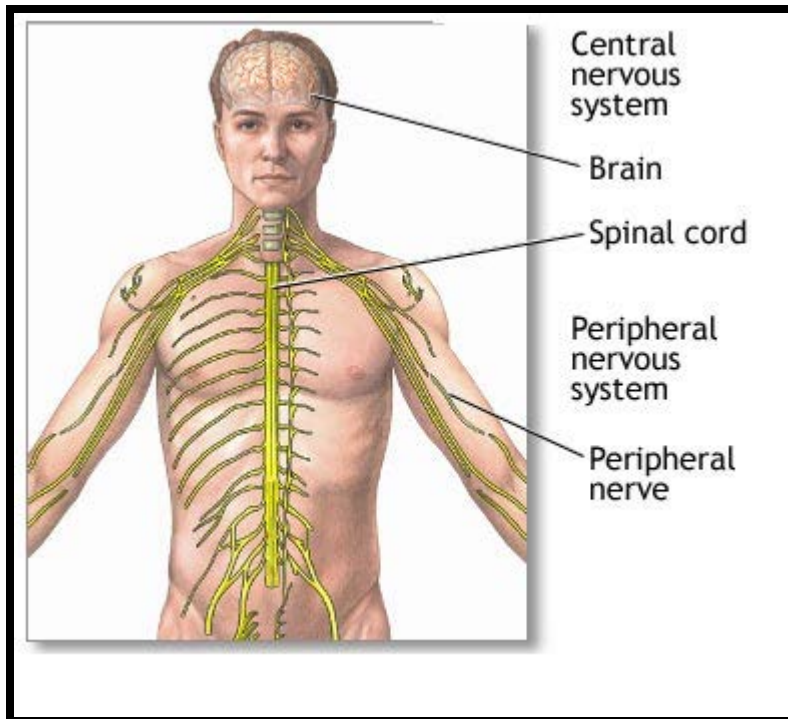
### **THE HUMAN NERVOUS SYSTEM**

In order for a drug to have psychoactive effects, it must enter the brain and change the functioning of that organ.

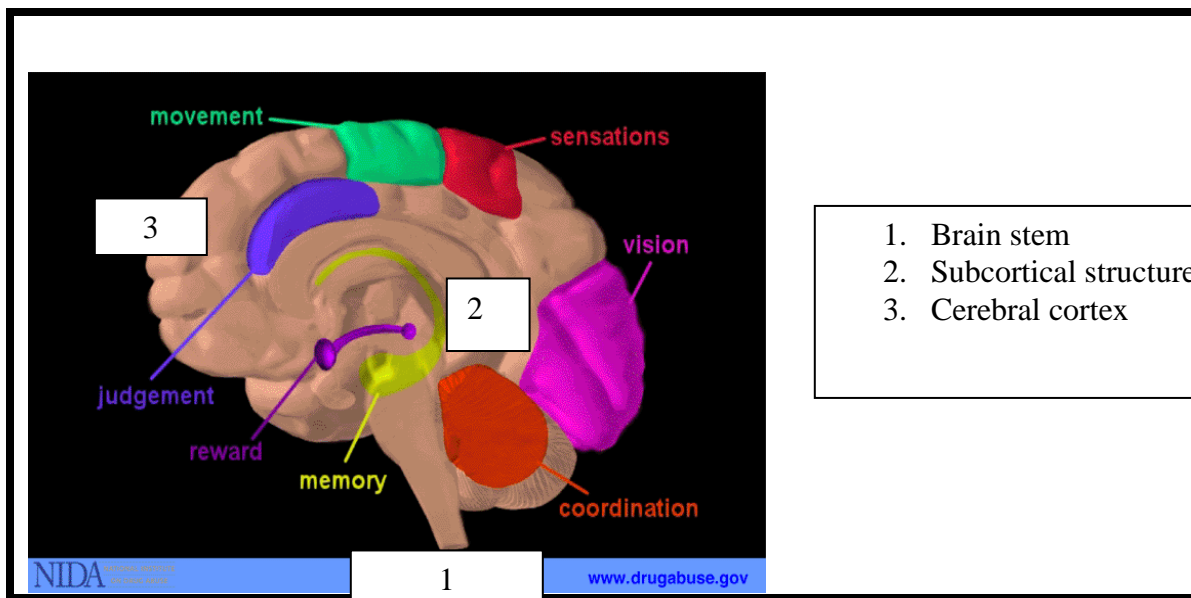
The nervous system can be divided into the **central nervous system (CNS)**, which includes the brain and spinal cord, and the **peripheral nervous system (PNS)**, which includes all of the nerves that extend from the spinal cord to the trunk and extremities (i.e., the arms and legs). Our concern here is going to be with the CNS.

---

<sup>1</sup> American Psychiatric Association (2000). Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Arlington, VA: American Psychiatric Association.



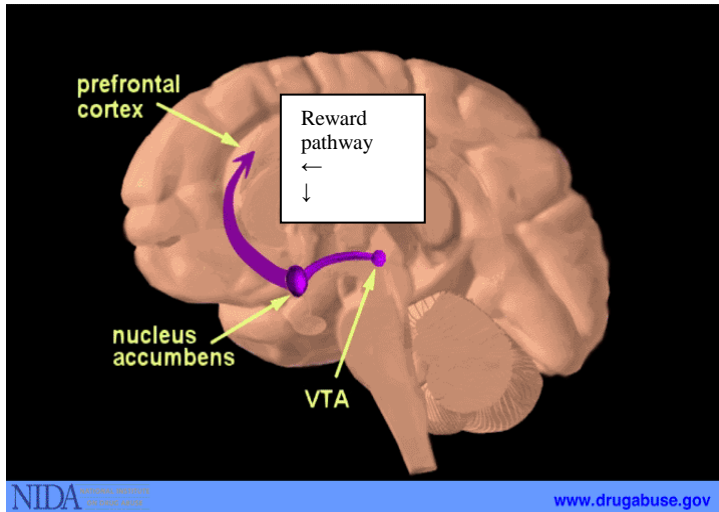
The brain itself can be roughly divided into three sections, the **brain stem**, the **subcortical structures** (which lie underneath the cerebral cortex) and the **cerebral cortex**, which wraps around the rest of the brain. Below is a graphic representation of the brain, sliced down the middle as we were looking at the person from the side.



As you can see, the brain stem is basically an extension of the spinal cord. Among other things, it controls autonomic (automatic) functions such as the breathing rate, pulse, vomiting and coughing. These are essential to survival, but they are not under conscious control, but they are not under conscious control. No one wakes up and says “I better get my heart going.” Although there *may* be

individuals who can start and stop his or her heart at will, they are very rare, and usually have undergone a lifetime of highly intensive training and practice.

The subcortical structures lie above the brain stem and below the cortex.<sup>2</sup> Among other things, the subcortical structures include areas that control hunger and thirst, reproductive functions and basic emotions such as fear and the sexual instinct. Most importantly, this part of the brain also contains the “reward pathway” or “reward circuit.” The illustration above shows this area in purple as a series of structures linked together. In other words, there are a number of different parts of the brain are linked together to form the reward system. In the graphic that follows, a more detailed picture of the reward pathway is shown.



The main function of the reward pathway is to signal to an animal that it is doing something that is linked to survival. So, for example, eating and sex stimulate or “turn on” the reward pathway, giving us a good feeling that we want to feel again. That’s a good thing, because without food, none of us would survive, and without sex, our species, our family name, our genes and our values would be lost.

In recent years, it has become clear that most (but not all) psychoactive drugs switch on the reward pathway. In fact, as we will learn later in this course, some drugs affect the reward pathway more powerfully than food, water, sex or any other of the natural rewards. As you can imagine, this can be very confusing to the brain, which has never experienced anything that was more “important” than survival behaviors.

Finally, we have the cerebral cortex, which is the most advanced section of the brain. The cortex has many different functions, such as:

1. Sensory input (vision, hearing, taste, smell and touch) is received and processed
2. Motor functions: Voluntary movement begins in this section.
3. Association: Allows different parts of the brain to communicate to solve or respond to input from inside or outside the body. For example, a child touches a hot stove, feels

---

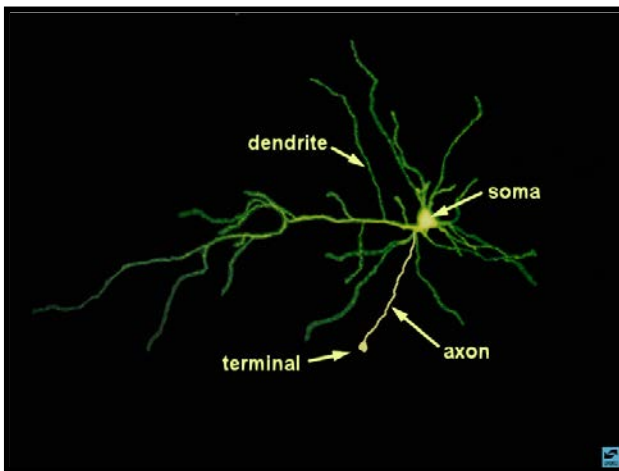
<sup>2</sup> It would also be correct to say that the cortex lies *outside* the rest of the brain since it wraps around the other structures and at times is actually lower in the body than other parts of the brain.

pain, removes his or her hand, and forms a memory of what happens when a hot stove is touched with a bare hand.

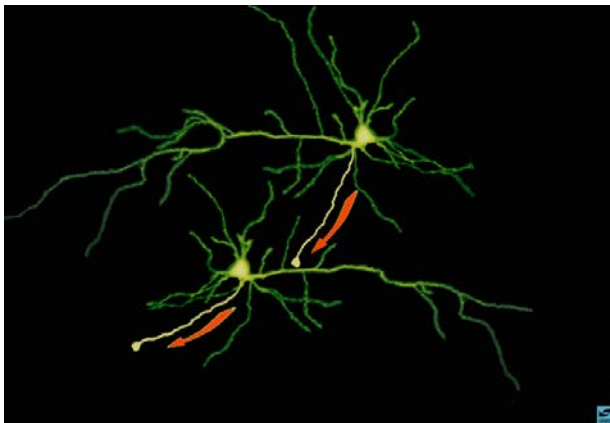
4. Executive functions; Abstract and rational thinking, control over impulses, empathy, conscience and spirituality seems to be important aspects of the **frontal cortex**.

Regardless of what part of the CNS one is looking at, all brain cells or **neurons** are constructed in the same way, and interaction between neurons and psychoactive drugs is necessary in order for the drugs to work.

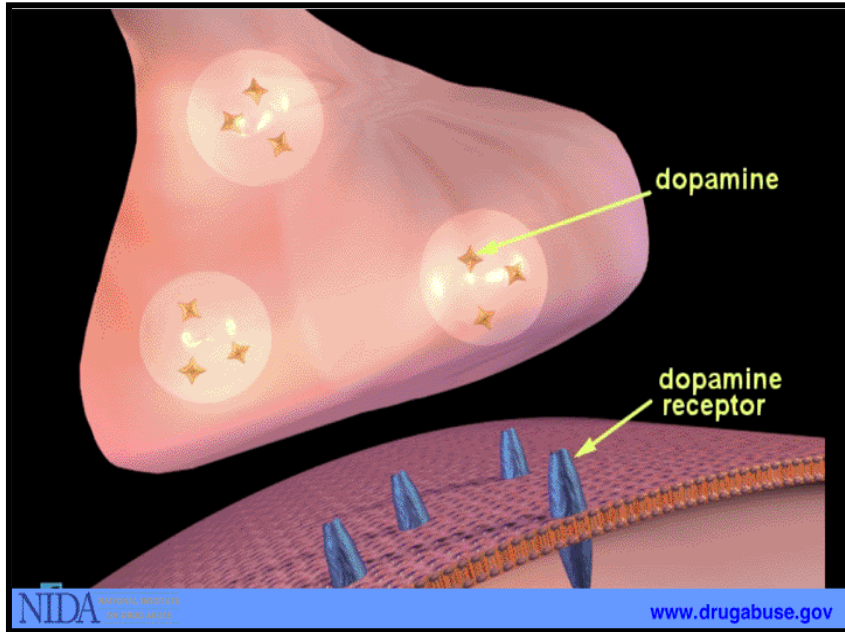
Below is an electron microscope picture of a single neuron. Note that the main portion of the neuron (the cell body) is called the **soma**. Leading to the soma are **dendrites**, which deliver input from other neurons and from the external (sights, sounds, smells, heat/cold) and internal (back pain, hunger pangs) environment. Leading from the soma is the **axon**, which carries nerve signals (“impulses”) to other neurons.



In the next photo, two neurons are shown, and red arrows show the direction of nerve impulses as they arrive and depart from the soma. When nerve impulses are traveling from one end of the neuron to the other, they are conveyed electrically. When they travel from one neuron to the other, they are sent chemically. We are going to focus primarily on the chemical **transmission**

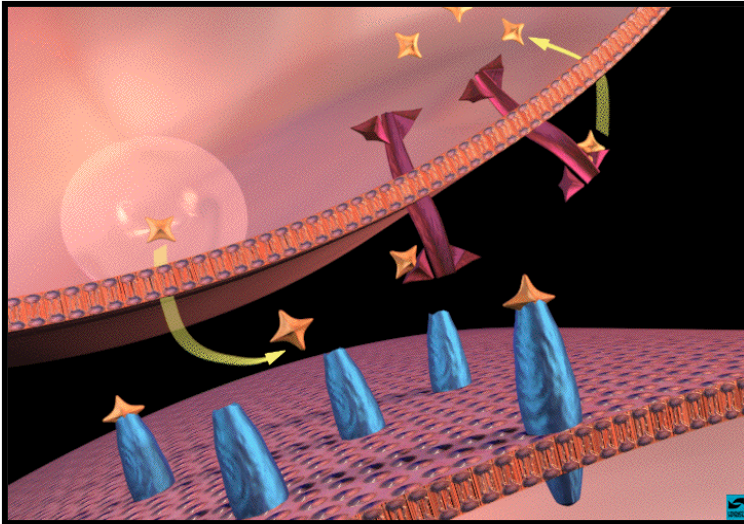


You can see that the axon comes to an end, and that there is a space between neurons. It may look like neurons actually touch, but they do not. The space between the first neuron's axon and the second cell's dendrite is called the **synapse**, **synaptic gap** or **synaptic cleft**. It is here that most psychoactive drugs work. The synapse lies between the end of an axon (this is called the **nerve terminal**) and the beginning of a dendrite. In this case, the neuron where the nerve terminal is located is known as the **pre-synaptic neuron** (it ends at the synapse) and the neuron to which the impulse is being sent is known as the **post-synaptic neuron**. Here is a graphic of the nerve terminal, the synapse and the post-synaptic neuron.



One of the things you can see in this illustration is that the dendrite contains a **receptor**. This is a docking site for the chemicals that carry messages across the synapse. These chemicals are called **neurotransmitters**, and in the picture above, there is a receptor for the neurotransmitter **dopamine**. Sometimes it is helpful for a person to think of the receptor as a lock and the neurotransmitter as a key. Only a certain key will open a lock, and only one neurotransmitter can fit into a receptor and cause a nerve impulse to be carried into the post-synaptic neuron.

In the picture that follows, dopamine is released from one neuron into the synapse. It then attaches itself to the dopamine receptor, which causes the nerve impulse to travel into the neuron that the receptor is attached to. After it has “done its job” the neurotransmitter is taken back into the releasing neuron, an action that it called **reuptake**. In a way, this is like a recycling program for neurotransmitters, since the dopamine can be reused.



Many psychoactive drugs work by imitating neurotransmitters. This is possible because a number of the drugs that people take to “get high” look (and are built) like neurotransmitters. For example:

<u>DRUG</u>	<u>NEUROTRANSMITTER</u>
Heroin	Endorphins (There are several)
LSD	Serotonin
THC <sup>3</sup>	Anandamide

Besides the neurotransmitters mentioned above, some others are:

- Acetylcholine
- Norepinephrine
- Glutamate
- GABA (gamma amino butyric acid)
- Dopamine

<sup>3</sup> THC= Tetrahydrocannabinol, the chemical in marijuana that causes the high



## REFERENCES

- Brick, J; Erickson, CK (1998). Drugs, the Brain and Behavior. New York: Hawthorn Medical Press.
- Cooper, JR; Bloom, FE; Roth, RH (2003). The Biochemical Basis of Neuropharmacology. New York: Oxford Press.
- Erickson, CK (2007). The Science of Addiction: From Neurobiology to Treatment. New York: WW. Norton
- Gold, MS (1994). *Clinical Implications of the Neurobiology of Addiction*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.
- Goldestein, A. (2001). Addiction: From Biology to Drug Policy (2<sup>nd</sup> Ed). New York: Oxford University Press.
- Hardman, JG & Limbird, LE (Eds) (2001). Goodman & Gilman's Pharmacological Basis of Therapeutics-10<sup>th</sup> Edition. Columbus, OH: McGraw-Hill.
- Morgan, JP (1994). *Principles of Pharmacology and Biopharmaceutics*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.
- National Institute on Drug Abuse. *The Brain & Actions of Cocaine, Opiates and Marijuana*. Retrieved October 10, 2006 from <http://www.nida.nih.gov/pubs/Teaching/>.
- National Institute on Drug Abuse. *The Neurobiology of Addiction*. Retrieved October 10, 2006 from <http://www.nida.nih.gov/pubs/Teaching/>.
- National Institute on Drug Abuse. *Understanding Drug Abuse and Addiction: What the Science Says*. Retrieved October 10, 2006 <http://www.nida.nih.gov/pubs/Teaching/>
- Steindler, EM (1994). *Addiction Terminology*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.
- Venes, T (2005). Tabor's Cyclopedic Medical Dictionary. Philadelphia: F.A. Davis
- Wilcox, RE; Gonzales, RA & Erickson, CK (1994). *Basic Science of Addiction*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.

# STREET DRUG PHARMACOLOGY

## PART II

In this section of the course, we will begin to examine the pharmacology of specific psychoactive substances. Before we start, it would be helpful to know that we will be focusing on five characteristics:

- Addiction potential
- Potential for physical dependence/severity of withdrawal symptoms
- Development of tolerance
- Immediate and long-term toxicity
- Acute and chronic psychiatric impairment

### Addiction Potential

As you learned in week one, addiction can be summarized by three necessary criteria and two optional criteria. Remember that these are informal criteria that summarize the formal diagnostic criteria for *substance dependence* found in the DSM-IV-TR, but they can not be used to diagnose substance dependency because they are not as precise as the DSM-IV-TR criteria. The necessary criteria are compulsive use, loss of control/inability to use with intent, and continued use despite negative or adverse consequences. The two optional criteria are physical dependence and tolerance. They are often but not always present when a person is suffering from substance dependence. Because it can be confusing to use the word *dependence* to describe both the disorder of substance dependence and the diagnostic criterion of physical dependence, we will refer to substance dependence as *addiction*.

Determining addiction potential involves asking several questions:

1. What percentage of first-time users will enjoy the effect of the drug enough that they will seek it out again?
2. If an individual uses the drug on a regular basis, how likely is it that s/he will become dependent on the substance?
3. After being introduced to the drug, do sub-human animals (e.g., monkeys, rats, mice) seek out opportunities to self-administer the substance? Do they do so to the exclusion of eating, consuming water and engaging in reproductive behavior?
4. Does the drug stimulate the brain's reward pathway?

### Potential for physical dependence

Physical dependence refers to the need to continue using a particular drug on a regular basis to avoid withdrawal symptoms. When we use this term we are referring to the appearance of physically distressing and/or life-threatening symptoms when drug use is stopped suddenly. The substances that produce physical dependence are all CNS Depressants, such as *opiates*, *benzodiazepines*, *barbiturates* and other *hypnotic* (sleep-producing) drugs, and alcohol.

## Tolerance

The questions we will ask about each drug that we discuss are:

1. Does tolerance develop if the drug is used on a regular basis?
2. If tolerance does develop, how long does it take to do so?
3. What mechanism (e.g., enzyme induction, pharmacodynamic) is responsible for the development of tolerance?

## Immediate and Long-Term Toxicity

*Toxicity* is the degree to which a substance can cause physical damage to a person. As you can imagine, toxicity can happen on an *acute* or immediate basis (e.g., a fatal overdose on alcohol and prescription drugs) or a *chronic* or long-term basis (e.g., lung cancer caused by years of smoking tobacco). Some drugs produce primarily acute toxicity, some are more likely to produce long-term toxicity, and some result in both.

There is also a form of toxicity called *behavioral toxicity* this occurs when drug-related behaviors result in physical damage to the user. A good example of this would be a person who drinks, then drives. If the person stays home, there is a good chance that s/he would never be injured, but when alcohol and driving are combined, the potential for injury to the drinker as well as other driver's increases radically.

## Acute and Chronic Psychiatric Impairment

To use non-technical language, some drugs make people crazy. In other words, certain psychoactive substances produce psychiatric impairment. Sometimes the impairment shows up right away (within hours), and sometimes it takes weeks, months or years for psychiatric impairment to appear. Sometimes psychiatric impairment lasts for a few hours or days, and sometimes it persists for weeks, months or an indefinite length of time. Thus, we need to know which substances produce psychiatric problems immediately, and when it takes a longer period of time for this kind of problem to manifest itself. We also need to distinguish drugs that produce acute (short-term) psychological problems from those that produce chronic problems.

## **CNS Stimulants**

Recall that the letters "CNS" mean *central nervous system*, and that this refers to the brain and spinal cord. The drugs in the stimulant category all work by stimulating the CNS. Although there are a wide range of psychoactive substances in the stimulants group, all of them have similar characteristics.

The stimulants that we will look at include:

1. Amphetamines
2. Non-amphetamine medications
3. Cocaine
4. Khat/cathinone
5. Over the counter (OTC) medications

### **General Characteristics**

All stimulants increase or speed up the functions of the CNS. Pulse and breathing rates go up, blood pressure increases, there is a reversal of fatigue and higher level of alertness, and the appetite often decreases. The degree to which all of this happens depends on the type of stimulant, with over-the-counter (*OTC*) drugs producing mild to moderate effects, and controlled substances generating more powerful results.

### **Amphetamines**



**Illicitly manufactured amphetamine/"white cross"**



**Methamphetamine Powder**



**Crystal methamphetamine (“Crystal,” “ice”)**

Amphetamines are synthetic (man-made) drugs that are rarely used medically. Because today amphetamines are so rarely used in medicine, pharmaceutical companies do not make as many types of these drugs, nor do they manufacture them in the numbers that they did in the 1950s and ‘60s. As we progress into the 21<sup>st</sup> century, the type of amphetamine that is most prevalent in the United States is illegally-produced methamphetamine. However, since all amphetamines produce essentially the same effects, we can talk about them as a group.

Amphetamines can be taken orally (in the form of tablets, capsules or powder), snorted, injected or (in the case of crystal methamphetamine) smoked. Onset depends on the method of administration, but can range from 30 minutes or more in the case of ingestion to mere seconds when an amphetamine is injected intravenously or smoked. Duration of action also varies, but is always measured in hours. In general, amphetamines last 4-6 hours, but time-released forms have a longer duration of action. Reports that methamphetamine lasts 8-12 hours are both correct and incorrect. Peak

methamphetamine levels in blood occur at 3-4 hours. After that, many users (particularly those who are addicted) will consider the “high” over. However, purely physical effects (accelerated pulse, insomnia, loss of appetite) may persist for another 4 hours or more. So, how long does methamphetamine last? It depends on the user’s perspective.

During the 4-8 hours that amphetamine lasts, the user will experience pulse rates in excess of 100 beat per minute (bpm)<sup>4</sup>, often much higher, and an increase in breathing rate and blood pressure. S/he will feel alert, and fatigue (if present) will disappear. The user will also experience *anorexia* or lack of appetite<sup>5</sup>, even if no food has been eaten in days. Other physical effects include dilated pupils, tremor (mild shakiness), dry mouth (caused by *hyposalivation*- a decrease in saliva production), hyperactivity, sweating and *bruxism* (teeth grinding).

Although many people are familiar with methamphetamine, there are two other drugs in this category: amphetamine sulfate and dextroamphetamine. Methamphetamine is the most potent drug in this group. Illicitly manufactured methamphetamine appears on the street as a powder and as a crystalline substance (“meth crystal” or “crystal”) that can be smoked.



---

<sup>4</sup> Normal pulse rate in an adult is 60-100 bpm.

<sup>5</sup> Anorexia (lack of appetite) should not be confused with the psychological disorder anorexia nervosa. For information on the latter, visit the Johns Hopkins Medicine website ([http://www.hopkinsmedicine.org/Psychiatry/eating\\_disorders/faq.html](http://www.hopkinsmedicine.org/Psychiatry/eating_disorders/faq.html))



**Addiction Potential.** Although some people use amphetamines to lose weight or to battle fatigue, it is the psychological effect of these drugs that explains their high addiction potential. The amphetamines are one group of drugs that do this, and they do it very powerfully. Users will use words like “euphoria,” “elation,” “joy,” “self-confidence,” and “mastery” to describe the amphetamine experience. Other effects include the ability to focus and concentrate on written materials or other tasks, relief from boredom (including the boredom that is associated with repetitive tasks, such as assembly line work) and depression, and, in both males and females, an increase in *libido* (sex drive). Published research indicates that, all other things being equal, amphetamines increase libido more than any other drug, including cocaine).

Although the amphetamines have a high addiction potential, there are factors that decrease this effect. First, there are the side effects (tremor, bruxism, hyperactivity, nervousness, etc.). Then, there is the *crash* or rebound depression. When the psychological effects of amphetamines wear off, the user often feels let down or sad. In certain cases, the depression can be severe, even suicidal. “Despair,” “panic,” “anxiety,” and “unbelievable boredom” are all words that have been used by amphetamine users to describe the crash. There is often a craving for more of the drug, and a desire to recapture the high. In addition, certain physical effects (such as rapid pulse, tremor and insomnia) do not disappear until hours after the high wears off, making a bad situation even worse. In a situation like this, users have three different options:

1. Wait out the crash
2. Take more amphetamine
3. Use a sedating drug (e.g., alcohol, tranquilizers, opiates) to induce sleep as a means of escape.

If the user elects option #2, s/he will often need more amphetamine than before, since tolerance to this group of drugs can develop within a few days, depending on the dose. On the other hand, an occasional user may not always develop tolerance. Regardless, if the “run” (binge) is continued, the user will continue not eating or sleeping, in some cases for days at a time. Weight loss, malnutrition and sleep deprivation may result, and the person in question may become more susceptible to infections and other medical conditions. In addition, a paranoid psychosis may develop (this is discussed in the Psychiatric Impairment section below).

If the user decides to “soften” the crash with sedating drugs (including alcohol), there is always the risk of respiratory or cardiac arrest. Mixing stimulants and depressants can result in either of those outcomes. In addition, dependent users may become addicted to the sedating drug in addition to the particular amphetamine they are using.

**Tolerance.** Increasing doses of amphetamine and the frequency with which they are used will result in tissue tolerance or *desensitization*. Highly tolerant users may need to take ten times or more the amount of amphetamine that they initially used to “get high.” Although it can take weeks or months for a person using smaller amounts of amphetamine to develop tolerance, heavy users may find that they become desensitized to meth in a matter of days. When tolerance develops slowly, it often goes away slowly, and when it develops quickly, often disappears rapidly.

### **Physical Toxicity.**

Some psychoactive substances cause immediate toxicity (e.g., heroin overdoses), and some-like tobacco-are more likely to cause long-term toxicity. The amphetamines do both. On an acute (immediate) basis, use of the amphetamines can cause different types of “heart attack,” stroke, seizures and/or very high body temperature, all of which can cause serious damage to the body or even be lethal. Amphetamine-related emergency room visits reported to the Drug Abuse Warning Network (DAWN) accounted for about 6% of emergency room visits in 2006. This is in comparison to cocaine (31%), cannabis (15%) and heroin (11%).

On a more chronic basis, amphetamine use contributes to an elevated risk for infection and disease as the result of malnutrition and lack of sleep. In addition, dental problems (“meth mouth”) can occur in some users. Over a longer period of time, chronic amphetamine use may result in cardiovascular disease as well as changes in the structure and function of certain portions of the brain.



**Amphetamine-related oral disease (“meth mouth”)**

## **Psychiatric Impairment.**

We have already noted that amphetamine use often leads to rebound depression—the “crash.” In some cases, this depression is more persistent, and can develop into a chronic problem. In addition, recovering amphetamine addicts frequently suffer from *anhedonia*, an inability to experience pleasure from normally pleasurable pursuits (e.g., eating, sex, hobbies). This anhedonia usually diminishes over time, and will often disappear slowly over a period of 6 to 12 months.

A second major psychological problem produced by the amphetamines is the development of a paranoid psychosis. The amount of amphetamine and the length of use necessary to produce the psychosis varies, but it most commonly occurs when large amounts of the drug are used over a period of days. However, once the first psychosis occurs, subsequent episodes become increasingly likely even when smaller amounts of amphetamine are used and the binge is shorter in duration. A stimulant psychosis often begins with escalating feelings of irritability, suspicion and hostility. Later symptoms include *delusions* (beliefs without a basis in reality) of persecution, fearfulness, and visual, auditory and tactile hallucinations. The latter are hallucinations involving the sense of touch, and most often appear as the “coke bugs”: the perception that ants, spiders or insects are crawling on or under the skin<sup>6</sup>. Amphetamine users who experience tactile hallucinations often scratch their skin, and may try to remove the “bugs” from under the skins with their fingernails or even a small knife or nail file. This results in scratches, cuts and “scabs,” often on the face, hands and arms. The psychosis tends to go away as amphetamines leave the body, but may persist for a number of hours after the “high” is over. In some cases, a stimulant psychosis will last 24 to 48 hours after the user has stopped amphetamine use, but rarely longer. If the psychosis does persist for a longer period of time, psychiatric consultation should be sought. Currently, there is little evidence that transient (temporary) stimulant psychoses increase the risk of chronic mental health problems except among those who were at high risk for such disorders before using amphetamines. The same can be said of amphetamine-induced depression.

## **Non-Amphetamine, medically-prescribed stimulants**

Substances in this category act in a similar manner to the amphetamines, but may have a lower addiction potential. On the street, the most common of these substances is Ritalin. Here is a list of substances in this group with their generic and brand names.

- ◆ Benzphetamine (Didrex)
- ◆ Mazindol (Sanorex)
- ◆ Methylphenidate (Ritalin)
- ◆ Phenmetrazine (Preludin/Prelud-2)
- ◆ Diethylpropion (Tenuate)
- ◆ Phedimetrazine (Plegine/Bontril)

---

<sup>6</sup> Although tactile hallucinations are best known as “coke bugs,” they are caused by a variety of stimulants, including the amphetamines.

◆ Phentermine (Fastin)

## Cocaine

- coca (*Erythoxylum Coca*)
- cocaine hydrochloride (hcl) ("coke", "toot", "nose/nose candy", "blow", "freeze", "snow", "girl", "white lady", "la mujer blanca")
- alkaloidal cocaine ("free base", "crack", "rock/ready rock", "basuco")

While amphetamines are synthetic (man made), cocaine can only be found in the leaves of the coca plant, native to the highlands of South America. Other differences between cocaine and the amphetamines include:

- Cocaine is a short-acting drug, with a duration of 5-60 minutes.
- Cocaine can be snorted, injected or smoked, but it is relatively ineffective when swallowed. The exception to this rule is when a condoms or balloons filled with cocaine are swallowed (for the purpose of smuggling the drug) and then burst in the individual's stomach.
- Tolerance to cocaine can develop and then disappear in a matter of hours.
- When cocaine is snorted, it tends to do much more severe damage to the nasal area.
- Cocaine produces *local anesthesia* or numbness on areas where it is applied.

With the exception of these differences, cocaine and the amphetamines are very similar. Both are strong CNS stimulants and have: 1) a very high addiction potential; 2) the ability to produce both immediate and long-term toxicity; 3) the potential for "crashing" as well as persistent or chronic depression; 4) the ability to trigger a paranoid psychosis.

Cocaine appears on the street in two forms: *alkaloidal cocaine* (cocaine base) and cocaine hydrochloride (hcl) powder. Cocaine base can either be made from cocaine powder in a purified form ("free base") or purchased already converted to the base form ("crack," "rock," "ready rock").



### Cocaine Hcl/"coke"



### Cocaine base ("crack")

Cocaine hcl can be swallowed or injected, but tends to burn rather than *volatilize* (turn into a gas capable of being inhaled) when smoked. Cocaine base, since it is not water soluble (it does not easily dissolve in water), can only be administered by smoking. When cocaine is snorted, it lasts 30-60 minutes, while its duration is only 5-10 minutes when injected or smoked. However, smoked cocaine has a higher addiction potential than snorted "coke" because, in general, the faster the onset, the more pleasurable the high.

## **Non-Amphetamine, medically-prescribed stimulants**

Substances in this category act in a similar manner to the amphetamines, but may have a lower addiction potential. On the street, the most common of these substances is Ritalin. Here is a list of substances in this group with their generic and brand names.

- ◆ Benzphetamine (Didrex)
- ◆ Mazindol (Sanorex)
- ◆ Methylphenidate (Ritalin)
- ◆ Phenmetrazine (Preludin/Prelud-2)
- ◆ Diethylpropion (Tenuate)
- ◆ Phedimetrazine (Plegine/Bontril)
- ◆ Phentermine (Fastin)

## **Ephedrine**

For many years, ephedrine was freely available as an over-the-counter drug. However, its use in the production of methamphetamine has resulted in increased control over its availability. Currently, it is either a prescription item (but not a controlled substance) or available only through a pharmacist in most States. It has a chemical structure that is very similar to amphetamines, but is considerably less potent. For this reason, it has a lower addiction potential, less physical toxicity (both acute and long-term), and less likelihood of producing a stimulant psychosis. Still, it can be dangerous, especially if taken in large quantities or used by someone who will be extremely active physical. Each year, several deaths are associated to the use of ephedrine, but the number is insignificant compared to the number of people who die as the result of cocaine or amphetamine use.

## **OTC (Over-the-counter) Stimulants**

Stimulants in this category include:

- Caffeine
- Phenylpropanolamine (a common antihistamine)
- Pseudoephedrine

Like ephedrine, the OTC stimulants have effects similar to amphetamines and cocaine, but their potency. Addiction potential, risk of toxicity and potential for psychiatric impairment is much lower than the more potent stimulants.

Until the last 5-10 years, pseudoephedrine was available in a variety of OTC cold and allergy medications. Because it, like ephedrine, is commonly used to make illicit methamphetamine, it is a Schedule V substance, a non-controlled but prescription item, or available only after requesting it from a pharmacist and, often, signing a registration book. In some States (e.g., Illinois) there is a legal limit to the amount of pseudoephedrine that can be purchased by any one individual each year.

Caffeine, the most popular of the OTC stimulants in the United States, can produce a mild dependency. Unlike most other stimulants, though, abrupt discontinuation of caffeine intake can result in physical withdrawal symptoms, the most common of which is headache.

## SUMMARY

In this section of the course, we studied the CNS stimulants, ranging from the more powerful and addicting substances (e.g., cocaine, amphetamines) to other-the-counter drugs such as caffeine that have a much lower addiction potential and cause fewer health problems.

All stimulants have some degree of addiction potential, but the amphetamines and cocaine have an extremely high potential. Although abrupt cessation of stimulant use does not result in physically distressing or life-threatening withdrawal signs, this does not mean that this group of drugs carries a lower risk of producing dependency.

Tolerance to stimulants occurs when the dose is raised to produce a more intense high. The development of tolerance often takes weeks (or days in the case of heavy use), but can both develop and disappear much more quickly in the case of cocaine, a very short-acting stimulant.

Both immediate and long-range physical problems are a frequent result of stimulant use. Fatal overdoses from stimulant use are less common than they are as a result of sedative or opiate (e.g., heroin) use, but they are not uncommon. Some of the most common immediate and long-range physical problems associated with use of the stimulants are associated with the cardiovascular system (the heart and blood vessels).

Also of great concern are both acute and chronic psychiatric issues. Rebound depression (“crashing”) and the paranoid psychosis are immediate problems, whereas persistent depression is a long-range concern. In the case of methamphetamine, cognitive thinking) problems may also occur.

## REFERENCES

- Brick, J; Erickson, CK (1998). Drugs, the Brain and Behavior. New York: Hawthorn Medical Press.
- Busko, M. (2007). Depression and Suicide Risk Identified in Methamphetamine Users. *Medscape News*, September 8, 2008. Retrieved September 10, 2008 from <http://www.medscape.com/viewarticle/567341>.
- Cho, AK; Melega, WP (2001). Patterns of Methamphetamine Abuse and Their Consequences. *Journal of Addictive Diseases*, 21(1): 21-34.
- Connell, PH (1958). *Amphetamine Psychosis*. New York: Oxford University Press.
- Cooper, JR; Bloom, FE; Roth, RH (2003). The Biochemical Basis of Neuropharmacology. New York: Oxford Press.
- Di Chiara, G & Imperato, A (1988). Drugs Abused by Humans Preferentially Increase Synaptic Dopamine Concentrations in the Mesolimbic System of Freely Moving Rats. *Proceedings of the National Academy of Sciences*, 85(14): 5274-5278.
- Erickson, CK (2007). The Science of Addiction: From Neurobiology to Treatment. New York: WW. Norton
- GlaxoSmithKline (2007). *Dexedrine (Dextroamphetamine): Prescribing Information*. Research Triangle Park, N.C.: GlaxoSmithKline.
- Glennon, RA; Yousif, M; Naiman, N; Kalix, P (1987). Methcathinone: A new and potent amphetamine-like

agent. *Pharmacology, Biochemistry and Behavior*, 26: 547-551.

Glennon, RA; Young, R; Martin, BR & Dal Cason, TA (1995). Methcathinone ("cat"): An enantiomeric potency comparison. *Pharmacology Biochemistry and Behavior*, 50(4): 601-606

Gold, MS (1994). *Clinical Implications of the Neurobiology of Addiction*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.

Goldstein, A. (2001). Addiction: From Biology to Drug Policy (2<sup>nd</sup> Ed). New York: Oxford University Press.

Kramer, J (1969). Introduction to Amphetamine Abuse. *Journal of Psychedelic Drugs* (Now Journal of Psychoactive Drugs), 2(2): 8-13.

Hardman, JG & Limbird, LE (Eds) (2001). Goodman & Gilman's Pharmacological Basis of Therapeutics-10<sup>th</sup> Edition. Columbus, OH: McGraw-Hill.

Klag, MJ; Wang, N-Y; Meoni, LA; Brancati, FL; Cooper, LA; Liang, K-Y; Young, JH; Ford, DE (2002). Coffee Intake and Risk of Hypertension: The Johns Hopkins Precursors Study. *Archives of Internal Medicine*, 162(6): 657-662.

Morgan, JP (1994). *Principles of Pharmacology and Biopharmaceutics*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.

National Institute on Drug Abuse. *The Brain & Actions of Cocaine, Opiates and Marijuana*. Retrieved October 10, 2006 from <http://www.nida.nih.gov/pubs/Teaching/>.

National Institute on Drug Abuse. *The Neurobiology of Addiction*. Retrieved October 10, 2006 from <http://www.nida.nih.gov/pubs/Teaching/>.

National Institute on Drug Abuse. *Understanding Drug Abuse and Addiction: What the Science Says*. Retrieved October 10, 2006 <http://www.nida.nih.gov/pubs/Teaching/>

Paulus, MP; Tapert, SF & Schuckit, MA (2005). Neural Activation Patterns of Methamphetamine-Dependent Subjects During Decision Making Predict Relapse. *Archives of General Psychiatry*, 62(7): 761-768.

Rawson, RA, Washton, A, Domier, CP & Reiber, C (2002). Drugs and sexual effects: role of drug type and gender. *Journal of Substance Abuse Treatment*, 22(2):103-108.

Simon, SL; Richardson, K; Dacey, J; Glynn, S; Domier, CP, et. al. (2001). A Comparison of Patterns of Methamphetamine and Cocaine Use. *Journal of Addictive Diseases*, 21(1): 35-44.

Spitz, HI & Rosecan, JS (Eds.) (1987). *Cocaine Abuse: New Directions in Treatment and Research*. New York: Brunner/Mazel.

Steindler, EM (1994). *Addiction Terminology*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.

Stimmel, B (Ed), Gold, MS & Galanter, M (Guest Eds) (1987). *Cocaine: Pharmacology, Addiction and Therapy*. New York: Hawthorn Press.

Tims, FM & Leukefeld, CG (Eds) (1993). *Cocaine Treatment: Research and Clinical Perspectives*. NIDA Research monograph 135, Rockville: NIDA.

Tremblay, LK; Naranjo, CA; Cardenas, L; Herrmann, H & Busto, UE (2002). Probing Brain Reward System Function in Major Depressive Disorder: Altered Response to Dextroamphetamine. *Archives of General Psychiatry*, 59(5): 409-416.

U.S. Food and Drug Administration (1998). Over-the-Counter Drug Products Containing Analgesic/Antipyretic Active Ingredients for Internal Use; Required Alcohol Warning. *Federal Register*: 63(20): 56789-56802.

Venes, T (2005). Tabor's Cyclopedic Medical Dictionary. Philadelphia: F.A. Davis

Waston, AM & Gold, MS (Eds.) (1987). Cocaine: A Clinician's Handbook. New York: Guilford Press.

Wilcox, RE; Gonzales, RA & Erickson, CK (1994). *Basic Science of Addiction*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.

## STREET DRUG PHARMACOLOGY

### PART III: HALLUCINOGENS

All of the substances in these groups produce more changes in cognition (e.g., thinking) and perception (vision, hearing, smell, taste and touch as well as *proprioception*-the sense of body position, size and location in space) than the stimulants. At the same time, the hallucinogens produce less mood change than the stimulants do. Many hallucinogen users identify the tendency to experience hallucinations as their main reason for taking these drugs.

The most common hallucinogen, by far, is LSD. Psilocybin mushrooms or synthetic psilocybin is also an available drug in many parts of the U.S., but the buyer may also end up with grocery-store mushrooms treated with LSD. Drugs that are called peyote and mescaline are also sold “on the street” in the U.S., but they are, in fact, very rare. As you can see, the hallucinogens have a high “rip-off” or misrepresentation rate.

In general these are the essential characteristics of the hallucinogens:

- **Addiction Potential:** Much of what we know about the addiction potential of psychoactive drugs can be learned from animal self-administration studies. Subhuman animals (e.g., monkeys, rats, mice) will actively press a bar in their cage in order to obtain a dose of cocaine, methamphetamine, heroin, barbiturates and benzodiazepines (tranquilizers). They will even do work to obtain certain drugs, and will also ignore food, water and/or sexually receptive members of their own species if they have to make a choice between those rewards and some of the drugs listed above. Animals will not self-administer hallucinogens, and dependency among humans is also rare. In those limited cases in which a person does become dependent on a hallucinogen, s/he will not experience withdrawal symptoms other than the symptoms of craving, anxiety and/or depression that are observed in virtually all cases of drug withdrawal.
- **Tolerance:** Sensitization to the effects of hallucinogens develops quickly (i.e., within a matter of days). In the case of LSD, if an individual attempted to use the drug on consecutive days, the dose would need to be doubled within two days, and up to ten times the original amount taken by the fifth day. On subsequent days, intoxication would be difficult to achieve at any dose.
- **Toxicity:** All mood-altering drugs affect the body, if only to change brain chemistry temporarily. In some cases, psychoactive drugs are linked to persistent or permanent abnormalities in the structure and function of the brain. The hallucinogens do not appear to be *neurotoxic* (brain damaging) substances, yet research as well as clinical experience has shown that in some users, administration of these drugs appears to be linked to the development of psychiatric problems.

Beyond any changes in brain functioning the hallucinogens might be linked to, there is little or no evidence that hallucinogens cause either immediate or

chronic physical toxicity. However, the possibility of *behavioral toxicity*<sup>7</sup> can be anywhere from low to extreme, depending on the dose and the user. A person who takes LSD and stays home watching the walls melt will very probably be alive the next day. Put the same person behind the wheel of a car, and the possibility of physical harm to the user, not to mention the public, is much greater.

- **Psychiatric Impairment:** Almost by definition, hallucinogens produce temporary psychiatric impairment. The degree of this impairment, though, varies considerably. Some users simply experience amusing or benign hallucinations, and then return to a normal state of mind. Others become confused, frightened, anxious or even psychotic for a short period of time before “coming down.” These negative mood states are commonly known as “bad trips”, “freak outs” or “bummers.” They are more common among younger people, those who are emotionally unstable and individuals who are anxious about taking a hallucinogen.

Long-term psychiatric impairment as the result of hallucinogen use does occur, but is rare. Individuals who use hallucinogens frequently or for long periods of time as more susceptible to chronic psychiatric problems, as are those who are high-risk for mental illness (e.g., due to a family history of schizophrenia).

## INDOLE HALLUCINOGENS

### **LSD**

LSD (lysergic acid diethylamide) belongs to a chemical group known as *indole* hallucinogens. The term indole refers to the basic chemical structure of hallucinogens in this group. These drugs resemble the neurotransmitter serotonin in their chemical structure.

LSD is a semi synthetic drug, made from lysergic acid, a substance that is present in ergot, a grain fungus that typically grows on rye. In pure form LSD is colorless, odorless and mildly bitter. Although it is typically ingested, it can be administered in its liquid form by *intramuscular* (into a muscle) or *intravenous* (into a vein) injection. The ED<sub>50</sub> for adult humans is approximately 20 to 30  $\mu\text{g}$  (micrograms), which is roughly equivalent to 1/100,000 oz. However, most LSD users ingest 100-200  $\mu\text{g}$ , and 500  $\mu\text{g}$  is considered the upper limit of safety when given to a human under controlled, scientific circumstances for the first time. The precise LD<sub>50</sub> for LSD has never been established, but it is known to be extremely high. After oral administration, the initial effects of LSD can be felt at 30-40 minutes, with peak effects occurring at 60-90 minutes. Although the average LSD "trip" lasted 10-12 hours during the 1960s and early 70s, current reports indicate shorter durations, of 7-8 hours. The reason for this shift in pharmacologic

---

<sup>7</sup> Behavioral toxicity occurs when a drug produces behavior that is potentially dangerous. A person who takes LSD and stays home will probably not experience any physical problems, but the same person could be injured if s/he tried to drive a car.

pattern is unknown, but it may be related to the use of an LSD isomer other than d-LSD.

Not all LSD is psychoactive. There are actually four possible forms of LSD, called *isomers* (compounds that have the same number and kinds of atoms, but arranged in different ways). Of these, d-lysergic acid (lysergic acid diethylamide/LSD-25) is by far the most potent. This fact may explain why some substances that are technically LSD have little or no hallucinogenic effect.

Liquid LSD is virtually never seen on the street. Instead, it is mixed with another liquid (most commonly water) in order to dilute the drug sufficiently to allow it to be handled in non-microscopic amounts. The dilute liquid is then placed on a carrier, which then becomes the dosage form. In the early- to mid-60s, the predominant dosage form was the common sugar cube (leading to the archaic slang term "cubes"). The most common dosage form in the late 60s and early 70s was the tablet, of various sizes, shapes, and colors, sometimes imprinted with a symbol (e.g., "Berkeley Peace Acid"), number or word. Some of these tablets were very small, while others (e.g., "double-dome") were larger than common over-the-counter drugs such as aspirin. Occasionally, LSD was found in the form of capsules. From the mid-70s until the current era, three forms of LSD have predominated: tiny tablets, 2-3 mm in diameter ("microdot"), squares of paper, often imprinted with a symbol or character ("blotter") and squares of plastic or film (windowpane).



Different forms of "blotter acid"



LSD Tablets

Side effects of LSD include:

- nausea (rare, but may occur during first 30-60 minutes)
- slight increase in body temperature
- *mydriasis* (dilated pupils)

## Psilocybin

Note: Since the late forties, *ethnobotanists* (people who study the use of plants in various cultures) have identified at least 20 species of psychoactive mushrooms being used by nine native tribes in Mexico and Central America. Of these, only *Psilocybe* is linked to drug use in the United States. This mushroom family includes a number of different species, the best-known of which is *psilocybe mexicana*.

1. *psilocybe mexicana*
2. *psilocybe baeocystes*
3. *psilocybe cubensis*
4. *psilocybe yungensis*

Psilocybin (“shrooms”) may be found as either dried or wet/fresh mushrooms. It is considerably less potent (approximately 150-200 times less) than LSD. 5-10 mg (5,000-10,000 micrograms) is the lowest dose of psilocybin which produces noticeable effects. Typical dosage forms contain 20-100 mg of psilocybin. In Timothy Leary's experiments with Harvard seminary students, each individual took 30 mg of the drug. Tolerance to psilocybin develops, but not as rapidly as it does in the case of LSD. There is *cross-tolerance* between LSD and psilocybin, i.e., the use of either of these drugs results in increased tolerance for both.

In addition, a form of synthetic psilocybin exists, but it is both rare and expensive.



Freshly picked psilocybin mushrooms



Dried psilocybin mushrooms

## CATECHOLAMINE HALLUCINOGENS

Note: The availability of both of hallucinogens in this group is so minimal in most parts of the United States that virtually all drugs sold as "peyote" or "mescaline" (organic or synthetic) are misrepresented. In the case of alleged mescaline, the actual chemical content of the drug is often LSD.

Drugs in this category resemble the catecholamine neurotransmitters norepinephrine, epinephrine and dopamine. They have slightly more ability than the indole hallucinogens to produce mood changes, but not to the extent of their chemical cousins, the amphetamines.

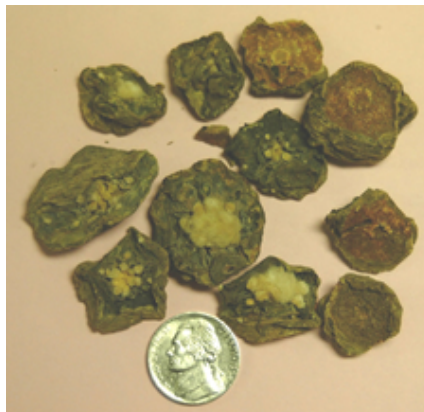
### **Peyote (*Lophophora williamsii* Lemire)**

Peyote is a cactus native to northern Mexico and the southwestern United States. It contains mescaline, which is the psychoactive ingredient. Although peyote is a schedule I substance, it may legally be used in traditional rituals by individuals who are born into the Native American Church of North America.

The "buttons" or growths of the peyote cactus are ingested. They may be taken in their natural form, or the buttons may be brewed into a tea and ingested in that manner. The taste and smell of peyote preparations is usually described as very unpleasant, with some would be users experiencing nausea and vomiting even before ingesting the drug. Three to six "buttons" is an average hallucinogenic dose, although some Native Americans may take up to thirty.



Peyote Cacti



## Peyote “Buttons”

### Mescaline

Although, as noted above, mescaline (“mesc”) is very rare “on the street”, there are technically two forms:

1. Organic mescaline, derived from the peyote cactus
2. Synthetic mescaline (3,4,5-trimethoxyphenethylamine)

At 180-220 mg, the effects of mescaline are primarily euphoric. At 300-400 mg, hallucinations predominant.

### ANTICHOLINERGIC SUBSTANCES

*Acetylcholine* (ACh) is another neurotransmitter. Substances that block the effects of acetylcholine are known as *anticholinergic*. Two of these substances, *atropine* and *scopolamine* are found in plants such as *Atropa belladonna* and *Datura Stramonium*. Common names for such plants include Jimson Weed, Nightshade, Angel’s Trumpet, Thorn Apple, Mandrake, Henbane and Loco Weed. Although some States (e.g., Nevada) consider these plants to be scheduled substances, federal law does not restrict or control access to them.

The effects of anticholinergic substances include:

- hallucinations
- increased or decreased activity level
- mood disturbance, possibly including anxiety, euphoria or depression
- language or speech impairment
- increased body temperature
- reddening of the face
- *dilated* (enlarged) pupils
- blurred vision
- dryness of the mouth
- *delirium* (decreased awareness of the environment, confusion or disorientation [especially of time], and memory impairment [especially of recent events])
- vivid and sometimes alarming hallucinations
- illusions and misinterpreted stimuli

These symptoms may be summed up with the expression, “Red as a beet, dry as a bone, blind as a bat and mad as a hatter.” Individuals under the influence of anticholinergic hallucinogens may become panicked, fearful, combative or self-destructive. Because of their severely altered mental state, it is difficult to “talk down” a person in this state. In addition, serious physical side effects, such as body temperature of 107° or greater, may require medical attention.

Because of these effects, anticholinergic substances have a slightly different profile than the other hallucinations:

**Addiction Potential:** As previously mentioned, hallucinogens have a low addiction potential, and anticholinergics are perhaps the less likely of the hallucinogens to be misused because of their unpleasant side effects.

**Toxicity:** The use of anticholinergics can result in death due to *hyperthermia* (high body temperature), *hypertension* (high blood pressure) or heart failure. Long-term toxicity caused by frequent use of these substances has received little study.

**Psychiatric Impairment:** Persons under the influence of anticholinergics may become severely disoriented “times three”; in other words, disoriented as to person, place and time. They also suffer from a lack of insight as to the reason for their abnormal psychological state. This is in contrast to the effects experienced by users of other hallucinogens, who often realize that they are under the influence of a drug. Frequent use of anticholinergics has been reported to result in persistent psychiatric impairment.



Jimson Weed



Nightshade

## SUMMARY

In this section of the course, we studied the hallucinogens, a group that includes both indole and catecholamine substances as well as the anticholinergics such as Jimson Weed. The indole hallucinogens resemble the neurotransmitter serotonin, while the catecholamines are more similar in chemical structure to norepinephrine.

The addiction potential of the hallucinogens is relatively low because they do not affect mood as much as they do cognitive processes. In addition, some people do not like the effects of hallucinogens, particularly ones ability to reality from fantasy. Hallucinogenic "trips" can produce fear, anxiety, depression and potentially long-lasting semi-psychotic effects.

Tolerance to the hallucinogens occurs very quickly, often in a matter of days, but also disappears quickly as well if the individual stops using one of these substances.

A more serious concern for hallucinogen users is immediate and long-range physical problems. In most cases, these problems are resolved quickly with medical intervention, but in a small number of users, they may persist for days, weeks or months.

Fatal overdoses from indole and catecholamine hallucinogens is very rare, and often the result of adulteration or behavioral toxicity. The anticholinergics have a high potential for physical side effects and even death.

## References

- Anon. (1975). "The Schizophrenia Epidemic," *Human Behavior*, October.
- Aberle, D. (1966). *The Peyote Religion Among the Navaho*. Chicago: Aldine.
- Albaugh, B. and Anderson, P. (1974). Peyote in the Treatment of Alcoholism Among American Indians. *American Journal of Psychiatry*, 131:1247-1250.
- Brown, Christine. (1972). *Hallucinogenic Drugs*. Springfield, IL: Thomas Publishing.
- Caldwell, W.V. (1969). *LSD Psychotherapy*. New York: Grove Press.
- Carroll, M.E. & Comer, S.D. (1994). *Phencycline and the Hallucinogens*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine
- Cohen, Sidney (1981). *The Substance Abuse Problems*. New York: Haworth Press.
- Ellis, H. (1897). A Note on the Phenomena of Mescal Intoxication. *Lancet*, 1:1540.
- Ellis, H. (1897). Mescal: A New Artificial Paradise. *Contemporary Review*, 73:130.
- Furst, P. (1972). *Flesh of the Gods: The Ritual Use of Hallucinogens*. New York: Praeger.
- Grilly, David (1989). *Drugs and Human Behavior*. Boston: Allyn and Bacon.

- Grinspoon, Lester (Ed.) (1990). "Psychedelic Drugs," *The Harvard Medical School Mental Health Newsletter*, 6(8), Cambridge, MA.
- Grof, Stanislav (1970). "The Use of LSD in Psychotherapy," *Journal of Psychedelic Drugs*, 3(1), September.
- Hoffer, A. and Osmond, H. (1967). *The Hallucinogens*. New York: Academic Press.
- Hoffman, A. (1980). *LSD: My Problem Child*. New York: McGraw-Hill Book Co.
- Howard, Judy, et. al. (1990). "Adaptive Behavior in Recovering Female Phencyclidine/ Polysubstance Abusers," in Spencer, John W. & Boren, John J. (Eds.), Residual Effects of Abused Drugs on Behavior, National Institute on Drug Abuse Research Monograph Number 101, Rockville, MD.
- Huxley, A. (1962). *Island*. New York: Harper & Row.
- Johnson, F.G. (1969). "LSD in the Treatment of Alcoholism," *American Journal of Psychiatry*, 126(1).
- Johnston, L. (1976). "Ford Signs Grant of \$750,000 in LSD Death in C.I.A. Test," *New York Times*, October 14, p. C43.
- LaBarre, W. (1974). *The Peyote Cult*. New York: Schocken Books.
- Loman, J. et. al. (1941). "Experimental Pharmacology of Postencephalitic Parkinson's Disease," *Transactions of the American Neurological Association*, 67.
- Ludwig, A.M. & Levine, J. (1967). "Hypnodelic Therapy," *Current Psychiatric Therapy*, 7.
- Ludwig, A.M., et. al. (1969). "A Clinical Study of LSD Treatment in Alcoholism," *American Journal of Psychiatry*, 126(1).
- Martin, A.J. (1967). "LSD Analysis", in Abramson, H.A. (Ed.), *The Use of LSD in Psychotherapy and Alcoholism*, Indianapolis: Bobbs-Merrill.
- Mathias, Robert (1993). "NIDA Takes a New Look at LSD and Other Hallucinogens," *NIDA NOTES*, March/April.
- National Institute on Drug Abuse (1992). LSD (Lysergic Acid Diethylamide). *NIDA Capsule C-92-01*.
- Pahnke, S., et. al. (1970). "The Experimental Use of Psychedelic (LSD) Psychotherapy," *Journal of the American Medical Association*, 212(11), June 15.
- Pahnke, S., et. al. (1970). "Psychedelic Therapy (Utilizing LSD) with Cancer Patients," *Journal of Psychedelic Drugs*, 3(1), September.
- Perry, C. (1985). *The Haight-Ashbury: A History*. New York: Vintage Books.

- Ray, Oakley S. (1972). *Drugs, Society, and Human Behavior (1st Edition)*, St. Louis: C.V. Mosby.
- Restak, Richard M. (1994). *Receptors*, New York: Bantam Books.
- Roseman, B. (1963). *The Peyote Story*. Hollywood, CA: Wilshire Book Co.
- Schultes, R. (1969). Hallucinogens of Plant Origin. *Science* 163: January 17.
- Schultes, Richard Evans & Swain, Tony (1976). "De Plantis Toxicariis e Mundo Novo Tropicale Commentationes XII. Further Notes on Virola as an Orally Administered Hallucinogen," *Journal of Psychedelic Drugs*, 8(4).
- Seymour, R. and Smith, D. (1987). *Guide to Psychoactive Drugs*. New York: Harrington Press.
- Senay, E. (1983). *Substance Abuse Disorders in Clinical Practice*. Boston: John Wright\*PSG Inc.
- Shick, J. Fred E. & Smith, David E. (1970). "Analysis of the LSD Flashback," *Journal of Psychedelic Drugs*, 3(1).
- Siegel, Ronald K. (1989). *Intoxication: Life in Pursuit of Artificial Paradise*, New York: E.P. Dutton.
- Slotkin, J. (1956). *The Peyote Religion*. Glencoe, IL: The Free Press.
- Stevens, J. (1987). *Storming Heaven: LSD and the American Dream*. New York: Harper & Row Publishers.
- Stockings, G. Tayleur (1940). "A Clinical Study of the Mescaline Psychosis, with Special Reference to the Mechanism of the Genesis of Schizophrenia and Other Psychotic States." *Journal of Mental Science*, 86.
- Strassman, Richard (1991). "Human Hallucinogenic Drug Research in the United States: A Present Day Case History and Review of the Process," *Journal of Psychoactive Drugs*, 23(1).
- Student Association for the Study of Hallucinogens (1973). "Mescaline," National Clearinghouse for Drug Abuse Information, Report Series 15 (1).
- Student Association for the Study of Hallucinogens (1973). "Psilocybin," National Clearinghouse for Drug Abuse Information, Report Series 16 (1).
- Thomas, Gordon. (1988). *Journey Into Madness: Medical Torture and the Mind Controllers*, Transworld Publishers, London, U.K..
- Wells, Brian (1974). *Psychedelic Drugs*, New York: Jason Aronson.

## STREET DRUG PHARMACOLOGY

### PART III: CNS DEPRESSANTS

CNS depressants are substances that depress or slow down the central nervous system, resulting in decreased breathing and pulse rates, lowered blood pressure and sedation. Opiates are one group of drugs in this category, but we will look at them separately because the use of heroin and other opiates is so common, and the medications used to either substitute for or antagonize opiates are specific to that category of drugs. In other words, methadone and buprenorphine are only used to treat opiate dependency, and with only one exception (alcohol) narcotic antagonists only work on opiates.

The three other categories of CNS depressants are:

1. Barbiturates and other *hypnotics* (medications used to induce sleep)
2. Benzodiazepines and other *anxiolytics* (medications used to treat anxiety)
3. Alcohol

Because alcohol is made and sold legally, it is not technically a street drug. For that reason, we will refer to it only in connection to its use with other CNS depressants.

Generally speaking, the CNS depressants are taken by mouth. They can be crushed and snorted or injected, but this is an uncommon practice. The intravenous injection of barbiturates in particular may result in serious infections at the site of injection. This is due to the irritating effect of this group of drugs as well as the difficulty of completely dissolving barbiturate tablets or the contents of barbiturate capsules.

#### **Hypnotics**

The hypnotic drugs include both barbiturates and non-barbiturate substances. All of these substances are controlled substances, but they fall into a number of schedules, depending on such factors as the currently accepted medical use, its potential as a drug of abuse, the duration of effect and the onset of action. For example, secobarbital (Seconal<sup>®</sup>) is a fast-acting barbiturate, and is in Schedule II. Phenobarbital, a slow-acting barbiturate, is in Schedule IV.

The barbiturate hypnotics ("barbs", "beans", "downers") include:

- secobarbital (Seconal<sup>®</sup>) ("reds")
- pentobarbital (Nembutal<sup>®</sup>) ("yellow jackets")
- apobarbital (Alurate<sup>®</sup>)
- mephobarbital (Mebaral<sup>®</sup>)
- phenobarbital (Luminal<sup>®</sup>)



Barbiturates

Barbiturates have a relatively long history, with the oldest (phenobarbital) being almost one hundred years old. Until the 1970s, they were the drugs of choice for inducing sleep. Unfortunately, they also became popular among those individuals inclined to commit suicide by overdose. Among the celebrities who died of barbiturate overdose (sometimes mixed with alcohol) are Marilyn Monroe, Dorothy Kilgallen (a noted reporter, columnist and television celebrity of the 1950s and 60s), Alan Ladd (a popular film actor of the 1940s and 50s), and the rock stars Jimmy Hendrix and Brian Jones.

The basic characteristics of barbiturates are:

1. Addiction potential moderate to high for all, with physical dependence possible.
2. Tolerance develops over a period of weeks or months, depending on the dose. Barbiturates show *cross-tolerance* with alcohol. This means that a person who has a tolerance for alcohol will also have a tolerance for barbiturates, even if s/he has never taken them, and vice versa.
3. Potential for immediate toxicity is moderate to high and very high when alcohol is also ingested. Potential for long-range toxicity is mild to moderate.
4. Potential for immediate psychiatric impairment is low, except during withdrawal. Potential for chronic psychiatric impairment is low.

Withdrawal symptoms associated with a physical dependence on barbiturates are the most serious of all the psychoactive drugs. Some physicians estimate that 25% of individuals with a physical dependence on barbiturates will die without medical intervention. In comparison, virtually no opiate dependent persons will die during withdrawal from that group of drugs.

Barbiturate withdrawal symptoms include:

1. *Tachycardia* (increased pulse rate)
2. *Hypertension* (high blood pressure)
3. *Diaphoresis* (sweating)
4. Abdominal and muscle cramps

5. Insomnia
6. Anxiety and irritability
7. Delusions
8. Hallucinations
9. Seizures (convulsions)

Medically supervised withdrawal from barbiturates is accomplished using either a long-acting barbiturate (e.g., phenobarbital) or one of the benzodiazepines (often Valium) to slowly detoxify the client. The practice of substituting a long-acting drug for a similar but short-acting drug in the same chemical family is very common. Besides using phenobarbital (which takes effect slowly but lasts almost twice as long as a short-acting barbiturate like Seconal or Nembutal) to “detox” barbiturate addicts, you have already seen that methadone is commonly substituted for the much shorter acting heroin. After the switch from a short-acting drug to a longer acting one, the amount of the drug is slowly reduced until the client is drug-free. This is just a part of treatment, however, since clients who are detoxed but not given counseling and assistance in finding self-help meetings often (but not always) relapse fairly quickly

There are also hypnotics that have many of the same characteristics as barbiturates, but are chemically different. Some of these are:

- triazolam (Halcion<sup>®</sup>)
- ethchlorvynol (Placidyl<sup>®</sup>)
- flurazepam (Dalmane<sup>®</sup>)
- estazolapam (ProSom<sup>®</sup>)
- profol injection (Diprivan<sup>®</sup>)
- tempazepam (Restoril<sup>®</sup>)
- quazepam (Doral<sup>®</sup>)
- zolpidem tartrate (Ambien<sup>®</sup>)
- eszopiclone (Lunesta<sup>®</sup>)
- ramelteon (Rozerem<sup>®</sup>)
- flunitrazepam (Rohypnol<sup>®</sup>/“roofies”)
- GHB/gamma hydroxy amino acid (Liquid G/Somatmax/G-riffic)

Two of the drugs listed above are not sold or used in the United States. These are flunitrazepam and GHB. Perhaps not coincidentally, both are also known as “date rape” drugs. Six more (triazolam, flurazepam, estazolapam, tempazepam, quazepam and flunitrazepam) are benzodiazepines<sup>8</sup>. As we will find out shortly, most “benzos” are used for daytime sedation, but the six listed above are used more often as hypnotics.

Generally speaking, the non-barbiturate hypnotics have the same characteristics as the barbiturates, although the benzodiazepine hypnotics do not produce the potentially life-threatening withdrawal symptoms that barbiturates do.

The effects of hypnotics are very similar to those produced by alcohol. They first produce sedation and relaxation as well as *disinhibition euphoria*, which can be defined

---

<sup>8</sup> Note that most of the benzodiazepines have generic names that end in “am.” Many end in “pam.”

as “Unrestrained behavior resulting from a lessening or loss of inhibitions or a disregard of cultural constraints” ([www.freedExceptionary.com](http://www.freedExceptionary.com)). In other words, that little voice in one's head that says “Don't talk; you'll just say something stupid” or “Don't do that or you'll look like a fool” gets turned down or silenced completely. Is this good? That depends on whether you're taking a chance at talking to someone you've never met before (probably a good thing) or starting an argument with someone who you think gave you a funny look at a party (probably not a good thing). Some people become happy and fun to be with when they become disinhibited, others become sad and still others become argumentative, aggressive and violent.

Just like alcohol, hypnotics also affect judgment, and use of these drugs may therefore be associated with impaired decision-making. With a larger dose, physical coordination is compromised, speech may become slurred, and activities that require judgment, timing, coordination and tracking (the ability to follow the course of a moving object) are impaired. Of course all of these effects depend on the dose and, to a lesser extent, set and setting.

As indicated in the introduction to this week's material, all CNS depressants decrease the user's breathing and pulse and lower his or her blood pressure. These effects become potentially life-threatening when: 1) a large dose of the drug is taken, or 2) the drug is mixed with alcohol. In essence, the risk is that the user's pulse and breathing will decrease to zero, at which point, of course, death occurs. When alcohol is mixed with other sedating drugs, a phenomenon called *potentiation* or *synergism* may occur. Synergism takes place when exposure to more than one drug chemical can result in health effects greater than expected when the effects of exposure to each chemical are added together. By way of illustration, let's assume that one drink of alcohol<sup>9</sup> has a CNS depressant effect of 1 and one capsule of Seconal also has a CNS depressant effect of 1. One might expect that combining the two would produce a CNS depressant effect of 2. However, when alcohol is involved, a *synergistic effect* occurs, and the mixture produces a CNS depressant effect of 3, 4 or even a higher number.

Another effect that can lead to death occurs when the user loses consciousness (“passes out”) on his or her back. If vomiting occurs, there is a good chance that what is being thrown up will not get out of the person's mouth, but will be *aspirated* (inhaled) into the respiratory tract, leading to suffocation. This possibility is made even more likely by the fact that the *gag reflex* (the tendency to choke and cough if a foreign object enters the respiratory system) is suppressed by most CNS depressants, so one of the body's chief defenses against suffocation is disabled.

Recently, a new series of hypnotics (Ambien, Lunesta and Rozerem) has become available. One of the major advantages of these newer drugs is that their use is associated with little or no hangover effect. In contrast, the dosages of other hypnotics prescribed for sleep often lead to grogginess the morning after they are taken.

Ambien works through specialized GABA *subreceptors* (specialized portions of a larger receptor; in this case, GABA), and has a potential for abuse. However, it is

---

<sup>9</sup> One drink = 12 ounces of beer, 4 ounces of wine or 1 ½ ounces of distilled spirits (vodka, rum, whiskey, etc.)

chemically unrelated to benzodiazepines, barbiturates and other hypnotics. Initially, few reports of Ambien abuse were published, but as time has gone by, these reports have increased. It has also become well known that some people who take therapeutic doses of Ambien engage in sleepwalking, and even sleep-cooking, eating and/or driving, but have no memory of these activities.



There are two forms of Ambien: regular release and extended release. The latter is prescribed for people who not only have trouble getting to sleep, but also awaken early in the morning and can not go back to sleep. The extended release form of Ambien has two layers, one of which acts immediately while the other dissolves several hours later.



Ambien (Regular release)



Ambien extended release

Lunesta, has an unknown mechanism of action, but is thought to also work through various GABA subreceptors. It also has an addiction potential, but the degree of this potential is unclear. Finally, Rozerem is a highly unusual hypnotic, which appears to

work through melatonin receptors. Melatonin is a neurotransmitter that is manufactured in the brain from serotonin, and is involved in regulating circadian rhythms (the 24-hour cycle of sleeping and waking) as well as physical responses to changes in seasons. In clinical testing conducted prior to the approval of Rozerem for human use, this substance showed no potential for abuse. In addition, it does not bind or attached to receptors that affect memory, balance, cognition, or respiratory depression.

## **Benzodiazepines**

Sometimes called minor tranquilizers (in contrast to the *neuroleptics* or major tranquilizers that are often used to treat major psychiatric disorders such as schizophrenia), the “benzos” are among the most commonly prescribed drugs in the U.S. Beginning with the creation of Valium and Librium in the 1950s, more than a dozen benzos are currently used in medicine, most often to relieve anxiety and treat anxiety-related disorders such as panic attacks.

Here is a fairly complete list of the benzodiazepines that are used for daytime sedation:

- chlorazepam (Tranxene<sup>®</sup>)
- chlordiazepoxide (Librium<sup>®</sup>)
- clonazepam (Klonopin<sup>®</sup>)
- diazepam (Valium<sup>®</sup>)
- oxazepam (Serax<sup>®</sup>)
- prazepam (Centrax<sup>®</sup>)
- alprazolam (Xanax<sup>®</sup>)
- lorazepam (Ativan<sup>®</sup>)

Prior to the discovery of the benzos, a less effective and more dangerous medication called meprobamate (Equanil<sup>®</sup>/Equagesic<sup>®</sup>/Miltown<sup>®</sup>) was often used to treat anxiety. Today, this drug is seldom prescribed.



10 mg Valium



0.25 mg Xanax

The basic characteristics of the benzodiazepines are very similar to the ones associated with barbiturates, except that:

1. The benzodiazepines' addiction potential is somewhat less.
2. Withdrawal from benzodiazepines is less serious than is the case with the hypnotics.
3. Immediate physical toxicity (in the form of overdoses) is less likely.

Virtually all the benzodiazepines are schedule IV drugs.

Before reading further, think about what might give one benzo a higher addiction potential than another.

What did you come up with? The first and foremost answer is onset of action. Across classes of drugs and with all other things considered, the ones that act the fastest also have the highest addiction potential. Below you will find a list of the benzos in order of their relative addiction potential.

### **Relative Abuse Potential**

alprazolam (Xanax)	higher
lorazepam (Ativan)	
clonazepam (Klonopin)	
diazepam (Valium)	↓
chlorazepate (Tranxene)	
oxazepam (Serax)	
chlordiazepoxide (Librium)	lower

According to this listing, Xanax has the highest addiction potential, and, in fact, it has the fastest onset.

Another factor that distinguishes one benzodiazepine from another is that severity of withdrawal symptoms. Once again, with everything else equal, the faster the effect of a drug wears off (the shorter the duration of action) the more serious the withdrawal symptoms will be. This is true of the opiates (methadone and buprenorphine withdrawal

is less severe than heroin withdrawal), hypnotics, benzodiazepines and most other drug categories. So, which benzo has the shortest duration? Again, the winner is Xanax.

Relative Severity of Benzodiazepine Withdrawal Symptoms

alprazolam		tremor (coarse @ high doses, fine <sup>10</sup> @ lower doses)
lorazepam		tachycardia/hypertension (↑ pulse/BP)
triazolam	severity	
Oxazepam	↑	delirium
flurazepam		seizures
clonazepam		diaphoresis (sweating)
diazepam		protracted tinnitus (a ringing or buzzing in the ears)
chlordiazepoxide		depression, with or without delusions

The withdrawal symptoms that appear above are associated with the use of high doses of benzodiazepines on a daily basis. There is another, more insidious type of physical dependency: low dose/long duration. This occurs when a person takes therapeutic doses of benzos for six months or longer. Abrupt discontinuation can result in fine tremor, insomnia, irritability, anxiety and difficulty concentrating. For this reason, doctors who understand the pharmacology of benzodiazepines will have their patients discontinue use slowly.

A final factor that you can use to differentiate one benzo from another is potency, which is determined by comparing the ED or ID of each drug in a particular category.

Benzodiazepine Dosage Equivalents (in milligrams/mg)

flurazepam (Dalmane)	30	lorazepam (Ativan)	2
tempazepam (Restoril)	30	alprazolam (Xanax)	0.5 - 1.0
chlordiazepoxide (Librium)	25	triazolam (Halcion)	0.5
oxazepam (Serax)	20-25		
chlorazepate (Tranxene)	15		
diazepam (Valium)	10		
clonazepam (Klonopin)	2		

**References**

Benzer, D.G. (1994). Management of Sedative-Hypnotic Intoxication and Withdrawal. *In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine.* Chevy Chase, MD: American Society of Addiction Medicine.

---

<sup>10</sup> Coarse tremor is noticeable trembling that makes everyday activities such as writing and holding a cup difficult. Fine tremor is a less severe and apparent trembling.

- Brick, J; Erickson, CK (1998). Drugs, the Brain and Behavior. New York: Hawthorn Medical Press.
- Busto, UE (1989). A Clinical Scale to Assess Benzodiazepine Withdrawal. *Journal of Clinical Psychopharmacology*, 9 (6): 412-16.
- Cooper, JR; Bloom, FE; Roth, RH (2003). The Biochemical Basis of Neuropharmacology. New York: Oxford Press. 85(14): 5274-5278.
- Erickson, CK (2007). The Science of Addiction: From Neurobiology to Treatment. New York: WW. Norton
- Gold, MS (1994). *Clinical Implications of the Neurobiology of Addiction*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.
- Goldstein, A. (2001). Addiction: From Biology to Drug Policy (2<sup>nd</sup> Ed). New York: Oxford University Press.
- Hardman, JG & Limbird, LE (Eds) (2001). Goodman & Gilman's Pharmacological Basis of Therapeutics-10<sup>th</sup> Edition. Columbus, OH: McGraw-Hill.
- Johnson, M.W.; Suess, P.E. & Griffiths, R.G. (2002). Ramelteon: A Novel Hypnotic Lacking Abuse Liability and Sedative Adverse Effects. *Archives of General Psychiatry*, 63: 1149-1157.
- Jones, I.R. & Sullivan, G. (1998). Physical dependence on zopiclone: case reports. *British Medical Journal*, 316:117.
- Jurgens, S.M. (1994). *Sedative-Hypnotics*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.
- Morgan, JP (1994). *Principles of Pharmacology and Biopharmaceutics*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.
- National Institute on Drug Abuse. *The Neurobiology of Addiction*. Retrieved October 10, 2006 from <http://www.nida.nih.gov/pubs/Teaching/>.
- National Institute on Drug Abuse. *Understanding Drug Abuse and Addiction: What the Science Says*. Retrieved October 10, 2006 <http://www.nida.nih.gov/pubs/Teaching/>
- Nowell PD, Mazumdar S, Buysse DJ, Dew MA, Reynold CF, Kupfer DJ. (1997). Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. *Journal of the American Medical Association*, 278:2170-2177
- Steindler, EM (1994). *Addiction Terminology*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.
- Tyrer P. (1993). Benzodiazepine dependence: a shadowy diagnosis. *Biochemistry Society Symposium*, 59:107-19
- Venes, T (2005). Tabor's Cyclopedic Medical Dictionary. Philadelphia: F.A. Davis
- Wilcox, RE; Gonzales, RA & Erickson, CK (1994). *Basic Science of Addiction*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.

## STREET DRUG PHARMACOLOGY

### PART V: OPIATES

NOTE: Opiates belong to a larger category of drugs known as CNS depressants. Other drugs in this group include alcohol, barbiturates and other *hypnotics* (sedatives), and the *benzodiazepines* (tranquilizers such as Valium, Klonopin and Xanax). These substances were discussed in a previous module.

The opiates are among the earliest drugs ever consciously used by humans. Reports of opiate use and cultivation go back at least 4,000 years. Ironically, several types of naturally-occurring opiate substances are found in the human body, primarily in the brain and digestive system. These internal opiates are known as endorphins or enkephalins. Since there are naturally-occurring opiates in the brain, it makes sense that there are also opiate receptors there as well. In fact, there are four types of opioid receptors, and the various internal and external opiates link up to them with various degrees of affinity (attraction). This explains why some opiates can be displaced from (removed from) their receptors by other opiates. The opiate receptor that appears most responsible for facilitating the effects of heroin is the mu ( $\mu$ ) receptor.

#### Narcotic (Opiate) Agonists

Although many different types of drugs are mistakenly called “narcotics,” this term only applies to opiates, drugs that fit into one of these categories:

1. Derived (taken from) opium (natural opiates)
2. Made from substances removed from opium (semi-synthetic opiates)
3. Created in laboratories to look like (have the chemical structure of) substances derived either directly or semi-synthetically from opium.
4. Bind to (attach to) opiate receptors in the brain.

A substance that binds to the brain’s opiate receptors and activates them (causes a change in the neuron that the receptor is part of) is called a *narcotic agonist*. There are three basic characteristics of these agonists:

1. They relieve pain
2. They are sedating
3. They produce *euphoria* (a sense of joy, happiness and/or well-being)

These are the basic characteristics of opiates:

- Addiction potential high
- Tolerance develops to the intoxicating dose, but not to the lethal dose
- Physical dependence is possible, and likely if daily use occurs.
- Physical toxicity level is high. Morphine overdoses<sup>11</sup> are among the most

---

<sup>11</sup> Because heroin is metabolized into morphine, heroin overdoses are noted by coroners

common fatal drug reactions in the United States

- Other types of physical toxicity are unlikely unless the opiate is impure (e.g., street heroin)
- Psychiatric impairment potential is low

Recall that there are natural, semi-synthetic and synthetic opiates. The natural opiates include opium and three substances that can be extracted from opium<sup>12</sup>:

- Morphine
- Codeine
- Thebaine
  - ◆ Thebaine does not produce the euphoria and sedation that opiate users seek. In fact, it can produce a rather unpleasant effect, and so it is not abused. However, it is the source for the semi-synthetic opiate Vicodin.

The semi-synthetic opiates are derived from morphine, codeine or thebaine, and include:

- Vicodin (hydrocodone)
- Heroin (diacetylmorphine)
  - ◆ Although Vicodin is widely used as an analgesic in cases of mild to moderate pain, heroin is a schedule I substance in the U.S. and is illegal for anyone, including a physician, to possess.

There are many synthetic opiates, all of which are created in laboratories. These include:

- Demerol (meperidine)
- Dilaudid (hydromorphone)
- Percodan/OxyContin (oxycodone)
- Numorphan (oxymorphone)
- Sublimaze (fentanyl)
- Methadone (dolophine)
- Diphenoxylate/atropine (Lomotil)
  - ◆ Some of these synthetic opiates (e.g., Fentanyl) are hundreds of times more potent than heroin. Another synthetic opiate, carfentanil (which was used in the 2002 Moscow theatre crisis to subdue Chechen terrorists) is 7000 times more potent than morphine.

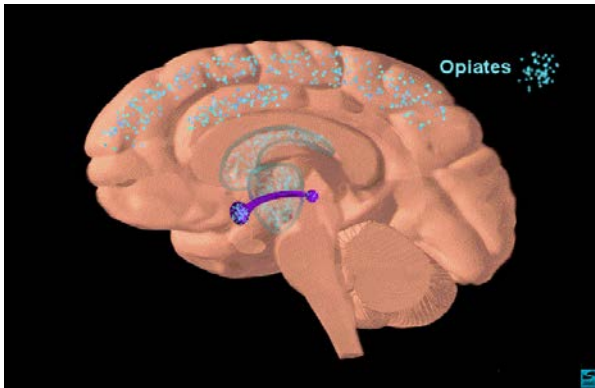
An unusual opiate concoction is “Karachi.” This mixture of drugs was sold in Chicago, but few, if any, other places. It is not as common now as it was in the 1990s. Karachi usually contains an opiate (e.g., Methadone) and a sedative (e.g., diazepam/Valium or phenobarbital).

Here is a graphic that shows the areas of the brain that opiates affect. You will notice that the reward pathway (in purple) is one of those areas.

---

or medical examiners as morphine reactions.

<sup>12</sup> Opium itself is rarely if ever seen in the United States



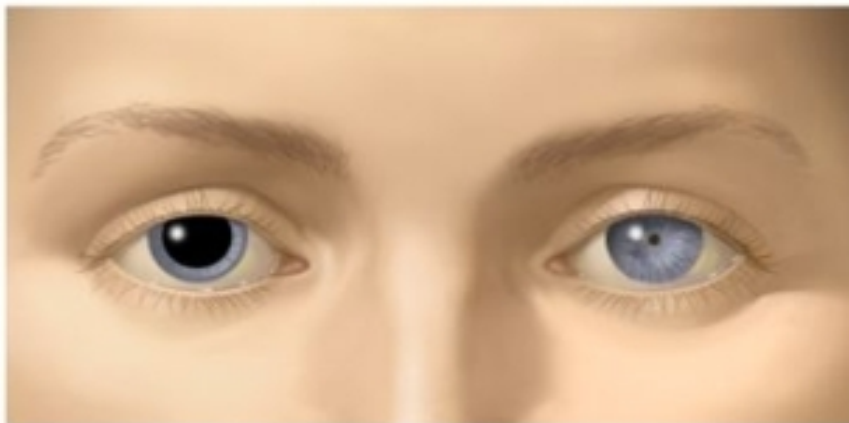
In addition to the triad of analgesia, sedation and euphoria, other effects produced by opiate agonists include:

- Reduced intestinal action (constipation)
- Relief from anxiety
- Increased (slower) reaction time
- Decreased breathing, pulse, blood pressure
- Reduction in *libido* (sex drive)
- Increase in threshold for aggression (Someone under the influence is less likely to be aggressive or violent).
- Constricted (small) pupils

Here is a graphic of dilated (large) versus constricted (small) pupils. Ordinary pupil size should be in between these two extremes.

Dilated pupil

Constricted pupil



Opiate addicts like to be “on the nod” or “nodding.” This state is not sleep, although the user is sedated and sleepy. It is not like being fully awake, either. Nodding is a point halfway between sleep and alert wakefulness. Often the user’s head will nod back and forth as s/he drifts between these two states, perhaps experiencing “waking dreams” that are both vivid and pleasant. The Greek poet Homer wrote of opium in *The Odyssey*. In one section of the epic story, Telemachus is depressed after failing to find his father Odysseus. But then Helen...

*"...had a happy thought. Into the bowl in which their wine was mixed, she slipped a drug that had the power of robbing grief and anger of their sting and banishing all painful memories. No one who swallowed this dissolved in their wine could shed a single tear that day, even for the death of his mother or father, or if they put his brother or his own son to the sword and he were there to see it done..."*

### Narcotic (Opiate) Antagonists

Have you ever gone to the hardware store to have a new house key made, then found when you got home that it fit into the lock but did not open it? Narcotic antagonists are similar to such keys. They are substances that bind to (occupy, fit into) the opiate receptor site but do not produce any kind of active effect. Since many opiate antagonists have a higher affinity (attraction to) opiate receptors than agonists, they can:

1. Displace an agonist (like heroin) from the receptor site
2. Block agonists from producing an opiate effect.

In a very real sense, having an opiate antagonists in the body is like having a badly made house key that keeps a working key from getting into the lock. As long as the imperfect key is in the lock, the working key can not fit into and open the lock. Antagonists block the effects of opiates by binding to receptors without stimulating them. If an antagonist is given to a person who is overdosing on an opiate (like heroin), the antagonist will displace the opiate from the receptor, keep it from reattaching, and reverse the overdose. However, if the person being given the antagonist is physically dependent on opiates, s/he will go into immediate withdrawal.

There are two types of narcotic antagonists:

- Full: No agonist effect. Completely blocks opiate receptors
  - Naloxone (Narcan)
  - Naltrexone (Rivea)
- Partial: Agonist effect at low doses and an antagonist effect at higher doses.
  - Talwin (pentazocine)
  - Talwin-NX (pentozocine with naloxone)
  - Nubain (nalbuphine)
  - Buprenorphine (Buprenex)

- Buprenorphine (Subutex®-buprenorphine sublingual<sup>13</sup> tablets)
- Buprenorphine (Suboxone®-buprenorphine and naloxone sublingual tablets)

It may seem hard to understand how a drug can have an agonist (morphine-like) effect at one dose and an antagonist effect (anti-morphine) as a higher dose. In short, this seemingly paradoxical effect is produced by the antagonist's affinity for different opiate receptors at different dosages. We will take a closer look at one of the partial antagonists- buprenorphine-when we get to pharmacological treatment of opiate dependence.

### Heroin (“smack”, “junk”, “H”, “doojee”, “stuff”)

Junk is the ultimate commodity, the merchandise is not sold to the consumer- the consumer is sold to the merchandise. Junk is the ideal product ... the ultimate merchandise. No sales talk necessary. The client will crawl through a sewer and beg to buy.

- Author and sometime heroin addict William S. Burroughs



Tan and white heroin

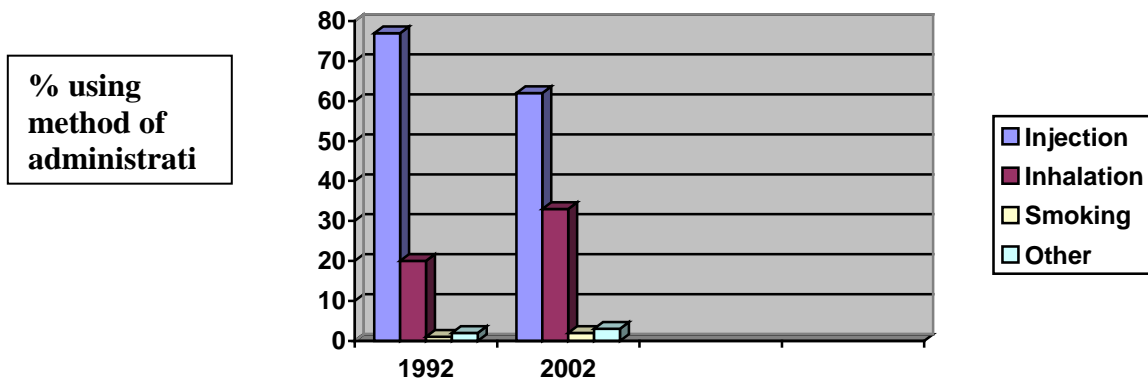
---

<sup>13</sup> Sublingual medication is placed under the tongue



Black tar heroin/"el chicle" (Spanish)

Heroin is the most commonly used illicit opiate. It appears as a white, tan or brown powder or as a black tar-like substance. Heroin is effective when swallowed, snorted, smoked or injected. It is seldom taken by mouth, and some forms (e.g., black tar) can not be snorted. Although heroin has typically been injected intravenously, the increasing purity of the drug in recent years (from 2-4% in the 1980s to 25-30% since the 1990s) has led to a decrease in injection and an escalation in snorting and smoking. Clearly, even at 30% purity or higher, the majority of street heroin is not heroin. Among the adulterants in street heroin are quinine, powdered chocolate, talc (talcum powder), baking soda, and other drugs. In some cases bacteria and other toxic substances are found in heroin, lending truth to the slang name, "junk."



Method of Heroin Administration, 1992 Vs. 2002

The injection of heroin may involve using non-sterile syringes and other paraphernalia (the user's "rig" or "works"). Diseases that can be transmitted through dirty syringes, "cookers" (often a spoon or bottle cap that is used to heat the heroin, melt it and mix it with water) and other paraphernalia include HIV, syphilis, and hepatitis B & C. Despite this fact, many users continue to use *i.v.* (intravenous) injection as their primary

route of administration. Reasons for this include:

1. Heroin is more effective at smaller doses when injected intravenously
2. I.V. injection produces a highly pleasurable “rush” which has been described as similar to an orgasm.
3. Some users enjoy the ritual of cooking the heroin, “tying off” (using a belt or rubber hose as a tourniquet), and “shooting” the drug.

The effect of heroin lasts 3-4 hours. Those who use the drug daily are highly likely to develop a physical dependence, and to experience withdrawal symptoms if their heroin use is abruptly stopped. The intensity and duration of opiate withdrawal varies depending on the specific drug involved, but typical symptoms include:

- Tearing (eyes shed water)
- Yawning
- Runny nose
- Restlessness
- Craving
- Nausea
- Vomiting
- Diarrhea
- Stomach, leg and back cramps
- Sweating
- Shivering
- “Goose bumps” (“cold turkey”)
- Insomnia
- Dilated (enlarged) pupils
- **Muscle and bone pain**
- Muscle twitching (“kicking the habit”)

One of the things you may have noticed is that opiate withdrawal symptoms are the opposite of the effects experienced when the drug is used.

<b>EFFECT OF USE</b>	<b>WITHDRAWAL SYMPTOM</b>
Constipation	Diarrhea
Constricted pupils	Dilated pupils
Sedation	Anxiety, restlessness, insomnia

The most intense signs of heroin withdrawal occur over a period of 3-4 days. Less severe symptoms (the Post-Acute Withdrawal Syndrome/PAWS) may persist for 6-12 months.

Below are the words of a song entitled “Cold Turkey” written by John Lennon, who was, of course, one of the Beatles. This is his impression of heroin withdrawal:

Temperature's rising  
Fever is high  
Can't see no future  
Can't see no sky

My feet are so heavy  
So is my head  
I wish I was a baby  
I wish I was dead  
Cold turkey has got me on the run

My body is aching  
Goose-pimple bone  
Can't see nobody  
Leave me alone

My eyes are wide open  
Can't get to sleep  
One thing I'm sure of  
I'm in at the deep freeze  
Cold turkey has got me on the run  
Cold turkey has got me on the run

Thirty-six hours  
Rolling in pain  
Praying to someone  
Free me again

Oh I'll be a good boy  
Please make me well  
I'll promise you anything  
To get me out of this hell  
Cold turkey has got me on the run

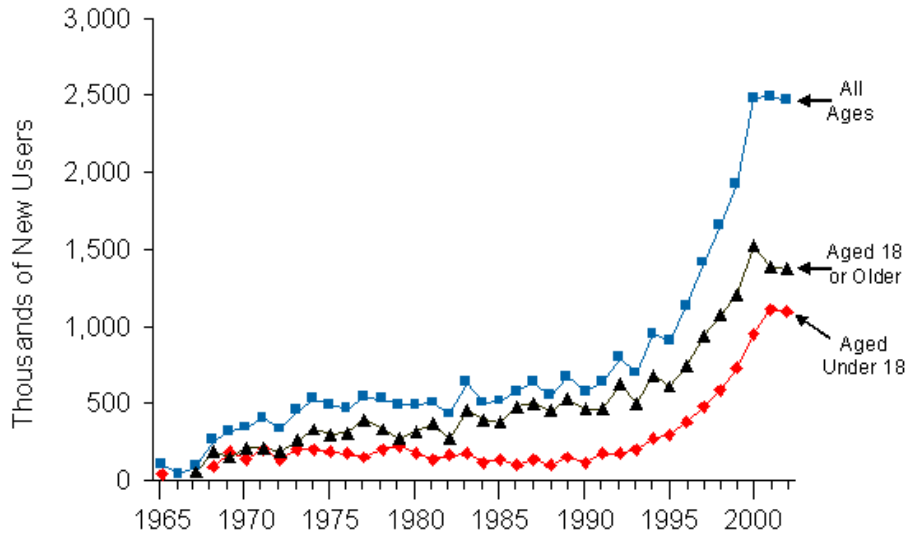
Although the use of pure heroin<sup>14</sup> has not been shown to produce medical complications, heroin users may suffer from physical problems related to:

- Local infection (infection at the site of the injection) and collapsed veins
- Systemic infection (infections carried through the blood stream to the heart and other organs and systems of the body)
- Impurities in the heroin resulting in bacterial infections and/or respiratory complications.
- Medical conditions related to the addict lifestyle (pneumonia, malnutrition, dental problems)

---

<sup>14</sup> In some countries, pharmaceutical heroin is used medically and/or can be obtained by registered addicts.

## Pharmaceutical Opiates



### Annual Numbers of New Non-medical Users of Opiate Pain Relievers: 1965–2002

As the chart above indicates, the non-medical use of opiate analgesics has increased significantly in the last 35-40 years. In fact, emergency room visits related to use of the pharmaceutical opiates has skyrocketed in recent years<sup>15</sup>.



### Percentage Increases in Hospital Emergency Department Visits Related to Use of Opiate Analgesics: 1995-2002

Still, in terms of actual numbers (not percentage increase), heroin overdoses are still much more prevalent than overdoses on pharmaceutical opiates.

One pharmaceutical opiate that has gotten a lot of press recently is OxyContin (oxycodone). Oxycodone has been used for years as a pain killer in cases of moderate to severe pain, and is well known under the brand names Percodan and Percocet. What

<sup>15</sup> Note that the “morphine” column actually represents heroin use

makes OxyContin different is that it is time-released, so that a very large dose of the drug is released over a period of 12 hours. Users often crush the tablets so that they get the entire dose all at once, leaving them at high risk of overdose. Opiate overdose is characterized by respiratory depression (seriously decreased breathing rate). The narcotic antagonists (particularly naloxone/Narcan<sup>®</sup>) are commonly used to reverse opiate overdose, and they do a good job. Unfortunately, some narcotic antagonists have a short duration of effect (e.g., 90 minutes), and when they wear off, the individual may go into respiratory arrest again.

### **Treatment of Opiate Dependency**

90% of opiate dependency treatment is the same as any other kind of chemical dependency treatment. The 10% that is unique is associated with the fact that opiates produce physical dependence, that fear of withdrawal symptoms is a strong motivator to keep using, and that there are specific and effective medications available to treat opiate addiction.

Medication can be used to:

1. Detoxify someone from opiates
2. Maintain someone on a less dangerous and addicting opiate
3. Ensure that a detoxified opiate addict can not get high from opiates

### **Opiate Detoxification**

Three drugs can be used to assist opiate-dependent clients in detoxifying:

1. Methadone
2. Buprenorphine
3. Clonidine<sup>16</sup>

In addition, methadone and buprenorphine can be used in “maintenance” programs as a substitute for heroin or other opiates.

### **Methadone**

Methadone is a synthetic opiate developed in the 1930s. Methadone has become the most widely used medication for opiate dependence treatment even though it has many of the same characteristics as morphine and heroin. The differences lies in the fact that methadone:

1. Suppresses opiate withdrawal symptoms for 24 hours rather than the 4-6 hours typical of heroin.
2. Has a higher affinity for opiate receptors than morphine, and so can, at a high enough dose, block heroin from attaching to that receptor. This dose is known as a “blocking dose.”

---

<sup>16</sup> Be sure not to confuse clonidine with the benzodiazepine Klonopin. The brand name of the latter was actually changed from Clonopin several years ago because of such confusion.

3. At methadone programs, is typically mixed with fruit juice and swallowed, and so taking it does not produce the “rush” that is characteristic of heroin injection.

Many people have noted that substituting methadone for heroin does not solve the problem of physical dependence because if the methadone is discontinued abruptly, withdrawal symptoms will appear. However:

1. Methadone only has to be taken once a day rather than the 4-6 times a day that one must use heroin in order to avoid withdrawal.
2. Methadone is not intended to produce an opiate high. Physicians in methadone program attempt to identify a dose that is high enough to alleviate withdrawal symptoms, but not so high that the client “nods.”

### **Buprenorphine**

Earlier, we discussed partial or “mixed” antagonists. Buprenorphine (“Bup”) is one of those drugs. At low doses, it acts like morphine, but at higher doses, is an antagonist.

Buprenorphine is capable of suppressing opiate withdrawal symptoms for 24 hours, just like methadone, but it is safer in a number of ways:

1. It has an “agonist ceiling” that ensures that after a certain dose has been reached, “bup” will produce no additional agonist activity.
2. It produces less respiratory depression than morphine or methadone, and so is less likely to cause overdoses. Administering even 100 times the normal dose of “bup” will not cause death.
3. It is less likely to produce a high than other opiate drugs.

As indicated above, “bup” is available in two forms, Subutex, which is a *sublingual* tablet (it goes under the tongue), and Suboxone, a sublingual tablet that contains both buprenorphine and naloxone. Wait a minute; naloxone is a full antagonist, and the gold standard for reversing opiate overdoses. Wouldn’t the naloxone produce withdrawal symptoms? This is the genius of Suboxone: naloxone is only effective as an antagonist when it is injected. If Suboxone is placed under the tongue like it supposed to be, the naloxone has no effect, but if the tablet is crushed and injected, the naloxone will precipitate immediate and severe withdrawal symptoms.

### **Clonidine**

Clonidine (Catapres<sup>®</sup>) is a drug used to treat *hypertension* (high blood pressure). It is not an opiate agonist or antagonist. So what does it have to do with opiate dependency treatment? In the 1980s, it was discovered that clonidine had the ability to suppress most opiate withdrawal symptoms. The reason for this is beyond the scope of this course, but it has to do with clonidine’s ability to calm a section of the brain that reacts to a “fight or flight” situation, in which an animal faces danger. Clonidine is not a maintenance drug, but it can be useful in detoxing opiate addicts from heroin in as little as 6-7 days, and methadone in as little as 14 days. However, if the client is on a methadone dose of more than 75 mg, the dose of clonidine needed to alleviate withdrawal symptoms may be so high that it produces significant *hypotension* (low blood pressure).

## Narcotic Antagonists

Another way of treating opiate dependency is to detoxify the client, then start him or her on naltrexone or another of the opiate antagonists. This will not diminish opiate craving because the antagonists occupy but do not activate neurons on which the receptors are located. What antagonists can do is to ensure that if the client, in a moment of impulsivity, decides to use heroin, the drug will not produce a high. This method of treatment requires a high level of compliance on the part of the client, because if s/he does not take the antagonist as prescribed, nothing bad or unpleasant will happen. This is a situation in which there is a moderate to high incentive to take the drug (i.e., the client will experience no high from opiates and so is less likely to relapse), but no immediate consequences. This situation is compared with opiate substitution therapy below.

<b>DRUG</b>	<b>Immediate incentive/Positive effect of taking the drug</b>	<b>Immediate consequence/Negative effect of not taking the drug</b>
Methadone	Relief from opiate withdrawal symptoms	Appearance of withdrawal symptoms
Naltrexone	Relief from drug craving	None

**Summary:** In this module, opiates have been described as central nervous system depressants with two special features. First, they are virtually identical to naturally occurring brain chemicals called endorphins. Secondly, they act as analgesics (pain-killers). While most opiates are scheduled substances, heroin is in schedule I, and so legally inaccessible to everyone, including licensed physicians. Overall, the opiates have a high potential for addiction and for immediate physical toxicity (in the form of overdoses). However, any long-term toxicity is due not to the effect of the drug, but to the addict lifestyle. For example, heroin use itself does not produce exposure to HIV or Hepatitis B or C; injection does. Heroin does not cause pneumonia; waiting for a dealer outside in the rain on a cold night does. Tolerance develops to the effects of opiates, and this phenomenon always precedes the development of physical dependence. On the other hand, opiates have a low potential for producing both immediate and chronic psychiatric impairment.

## References

Bowersox, J.A. Buprenorphine may soon be heroin treatment option. NIDA Notes 10:8-9, 1995.

Bowersox, J.A. Heroin update: smoking, injecting cause similar effects; usage patterns may be shifting. NIDA Notes 10:8-9, 1995.

Caplehorn, J & Dalton, M (1996). Methadone Maintenance and Addicts' Risk of Fatal Heroin Overdose, *Substance Use and Misuse*, 31(2): 177-196.

Cooper, J.R.; Altman, F.; Brown, B.S.; and Czechowicz, D., eds. Research in the Treatment of Narcotic Addiction: State of the Art. National Institute on Drug Abuse Monograph, DHHS Pub. # (ADM) 83-1281, 1983.

Dole, V.P.; Nyswander, M.E.; and Kreek, M.J. Narcotic blockade. *Archives of Internal Medicine*, 118:304-309, 1966.

Gevirtz, C; Subhedar, DV; Choi, CS (1998). Rapid Opioid Detoxification, *Journal of the American Medical Association*, 279: 1871.

Gold, MS (1993). Opiates. In *Principles of Addiction Medicine*, ASAM, Chevy Chase.

Goldstein, A. Heroin addiction: Neurology, pharmacology, and policy. *Journal of Psychoactive Drugs* 23(2):123-133, 1991.

Grella, CE; Anglin, MD; Wugalter, SE (1997). Patterns and Predictors of Cocaine and Crack Use by Clients in Standard and Enhanced Methadone Maintenance Treatment, *American Journal of Drug and Alcohol Abuse*, 23: 15-42.

Hughes, P.H., and Rieche, O. (1995). Heroin epidemics revisited. *Epidemiological Review*, 17(1):63-73.

Johnson, R.E.; Jaffe, J.H.; and Fudala, P.J. (1992). A controlled trial of buprenorphine treatment for opioid dependence. *Journal of the American Medical Association*, 267(20):2750-2755.

Kornetsky, C. Action of opioid on the brain-reward system. In: Rapaka, R.S., and Sorser, H., eds. Discovery of Novel Opioid Medications. National Institute on Drug Abuse Research Monograph 147. NIH Pub. No. 95-3887. Washington, DC: Supt. of Docs., U.S. Govt. Print Off., 1991, pp. 32-52.

Kreek, M.J. Rationale for maintenance pharmacotherapy of opiate dependence. In: O'Brien, C.P., and Jaffe, J.H., eds. Addictive States. New York: Raven Press, 1992, pp. 205-230.

Kreek, M.J. Using methadone effectively: achieving goals by application of laboratory, clinical, and evaluation research and by development of innovative programs. In: Pickens, R.; Leukefeld, C.; and Schuster, C.R., eds. Improving Drug Abuse Treatment. National Institute on Drug Abuse Research Monograph 106. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 245-266, 1991.

Kreek, M.J. (1996). Opiates, opioids and addiction. *Molecular Psychiatry* 1:232-254.

Lewis, J.W., and Walter, D. Buprenorphine: background to its development as a treatment for opiate dependence. In Blaine, J.D., ed. Buprenorphine: An Alternative for Opiate Dependence. National Institute on Drug Abuse Research Monograph 121. DHSS Pub. No. (ADM) 92-1912. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1992, pp. 5-11.

Marazzi, MA; Wroblewski, JM; Kinzie, J; Luby, ED (1997). *High-dose Naltrexone and Liver Safety*, *American Journal on Addictions*, 6:21-29.

Mathias, R. NIDA survey provides first national data on drug abuse during pregnancy. *NIDA Notes* 10:6-7, 1995.

National Institute on Drug Abuse. Epidemiologic Trends in Drug Abuse: Vol. 1. Highlights and Executive Summary of the Community Epidemiology Work Group. NIH Pub. No. 97-4204. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1997.

National Institute on Drug Abuse. "Heroin." NIDA Capsule. NIDA, 1986.

National Institute on Drug Abuse. IDUs and infectious diseases. *NIDA Notes* 9:15, 1994.

National Institutes of Health/National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction (1998). *Effective Medical Treatment of Opiate Addiction*, Journal of the American Medical Association, 280:1936-1943

Novick, D.M.; Richman, B.L.; Friedman, J.M.; Friedman, J.E.; Fried, C.; Wilson, J.P.; Townley, A.; and Kreek, M.J. (1993). The medical status of methadone maintained patients in treatment for 11-18 years. *Drug and Alcohol Depend* 33:235-245.

Nunes, EV; Quitkin, FM; Donovan, SJ; Deliyannides, D; Ocepek-Welikson, K; Koenig, T; Brady, R; McGrath, PJ; Woody, G. (1999 ). Imipramine Treatment of Opiate-Dependent Patients With Depressive Disorders: A Placebo-Controlled Trial, *Archives of General Psychiatry*, 55:153-160.

O'Connor, PG & Kosten, TR (1998). Rapid and Ultrarapid Opioid Detoxification Techniques, *Journal of the American Medical Association*, 279: 229-234.

Passaro DJ, Werner SB, McGee J, Mac Kenzie WR, Vugia DJ (1998). Wound botulism associated with black tar heroin among injecting drug users. *Journal of the American Medical Association*. 1998;279:859-863.

Rabinowitz, J; Cohen, H; Kotler, M. (1998). Outcomes of Ultrarapid Opiate Detoxification Combined with Naltrexone Maintenance and Counseling, *Psychiatric Services*, 49 (6): 831-833.

Senay, Edward C. (1998). *Substance Abuse Disorders in Clinical Practice* (2nd Edition), Norton & Co., New York.

Sobel, K. NIDA's AIDS projects succeed in reaching drug addicts, changing high-risk behaviors. *NIDA Notes* 6:25-27, 1991.

Shoji, Y; Delfs, J; Williams, JT (1999). *Presynaptic Inhibition of GABAB-Mediated Synaptic Potentials in the Ventral Tegmental Area During Morphine Withdrawal*, *Journal of Neuroscience*, 19(6): 2347-2355.

Sklair-Tavron, L; Wei-Xing, S; Lane, SB; Harris, HW; Bunney, BS; Nestler, EJ (1996). *Chronic morphine induces visible changes in the morphology of mesolimbic dopamine neurons*, *Proceedings of the National Academy of Sciences*, 93: 11202-11207.

Strain, E.C.; Stitzer, M.L.; Liebson, I.A.; and Bigelow, G.E. *Comparison of buprenorphine and methadone in the treatment of opioid dependence*. *American Journal of Psychiatry* 151(7):1025-1030, 1994.

Substance Abuse and Mental Health Services Administration. Preliminary Estimates of Drug Related Emergency Department Episodes: Advance Report Number 17. Rockville, MD: SAMHSA, 1996.

Substance Abuse and Mental Health Services Administration. "Preliminary Results from the 1996 National Household Survey on Drug Abuse." SAMHSA, 1997.

Swan, N. Research demonstrates long-term benefits of methadone treatment. *NIDA Notes* 9:1, 4-5, 1994.

Tai, B, Blaine, J. & NIDA Treatment Workgroup (1997). Naltrexone: An Antagonist Therapy for Heroin Addiction. National Institute on Drug Abuse, National Institutes of Health, November 12-13.

Uhl, G.R.; Kreek, M.J.; and Gorelick, D.A. (1995). Rates of Dopamine Transporter and Mu Opiate Receptor Occupancies, Cocaine and Heroin Reward, and Therapeutic Opportunities. Presented at Grand Rounds at the National Institutes of Health Clinical Center, Bethesda, MD.

Woods, J.H.; France, C.P.; and Winger, G.D. Behavioral pharmacology of buprenorphine: issues relevant to its potential in treating drug abuse. In: Blain, J.D., ed. *Buprenorphine: An Alternative for Opiate*

Dependence. National Institute on Drug Abuse Research Monograph 121. DHHS Pub. No. (ADM) 92-1912. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1992, pp. 12-27.

## STREET DRUG PHARMACOLOGY PART V: DISSOCIATIVE ANESTHETICS

*Dissociation* is a psychological process involving alterations in identity or sense of self. This often involves the separation of a group of mental processes from the rest of the thought processes, resulting in an independent functioning of these processes and a loss of the usual relationships. For example, there may be a separation of *affect* (mood) from *cognition* (thinking), in which case a person might know that they are going through a difficult and/or painful experience (e.g., rejection, grieving, trauma), but not feel any sadness, fear or anxiety. These alterations in sense of self can include a transient sense that the world or the self is "unreal" (derealization and depersonalization). In some cases, the individual will report that they can not figure out whether words they have heard were spoken by them, imagined or spoken by someone else.

A dissociative anesthetic is a substance that produces general anesthesia (a state of unconsciousness in which an individual is insensitive to pain or other unpleasant stimuli) characterized by *catalepsy* (a trancelike state with loss of voluntary motion and failure to react to stimuli), *catatonia* (a form of schizophrenia characterized by a tendency to remain in a fixed stuporous state for long periods alternating with short periods of extreme excitement), and amnesia, but not necessarily involving complete unconsciousness. The doses of the dissociative anesthetics (e.g., PCP, ketamine and dextromethorphan/"DXM") taken by people "on the street" do not generally produce a loss of consciousness, but varying levels of dissociation are often experienced. Although some users seek out these dissociative states, most prefer the detached, sedated and/or euphoric high produced by smaller doses of the drug. Users also report a sense of floating, and the facilitation of social interaction. This phase of intoxication is known as *disinhibition*. As dosage progresses, however, a large majority of users begin to experience confusion, disorientation, and difficulty concentrating or thinking clearly. They may also experience the onset of negative mood states, ranging from depression to disabling panic and psychotic paranoia, and from uncontrollable excitement to rigid, mute withdrawal.

Physical effects of dissociative anesthetics include:

- Nystagmus (involuntary rapid movements of the eyes vertically or horizontally)
- Hypertension (high blood pressure)
- Tachycardia (racing heartbeat)
- Dizziness and shakiness
- Drooling
- Dizziness
- Nausea
- Hyperthermia (increased body temperature)
- Anesthesia (reduced response to pain and other physical sensations)
- Slurred speech
- Excessive sensitivity to sound and light
- Ataxia (lack of muscle coordination)

- Catalepsy

More serious physical effects include:

- Seizures
- Dangerously high blood pressure (extreme *hypertension*)
- Breakdown of muscle and excretion of muscle proteins in urine
- Coma
- Death

Common psychological effects include:

- Disordered thinking and confusion
- Disorientation
- Impaired judgment
- Belligerence
- Aggressiveness
- Agitation
- Impulsiveness and unpredictability

More serious psychological effects include:

- Schizophrenic-like psychoses
- Hallucinations of sight, sound, or touch (not as common an experience as it is for hallucinogens such as LSD)
- Memory impairment

The general properties of dissociative anesthetics are:

- Addiction potential is low to moderate. Unpleasant side effects limit this potential.
- Tolerance develops over a period of weeks. The exact amount of time required to produce tolerance depends on the amount of the drug being used.
- The immediate physical toxicity potential is moderate to high. Although the dissociative anesthetics have a relatively high *therapeutic index* (a comparison of the amount of a drug that causes the therapeutic effect to the amount that causes toxic effects), the unknown quality of illicit/"street" versions of these drugs make overdosing a distinct possibility. In addition, a user may become confused or suffer impaired judgment and take more of the drug than s/he intended to.
- Acute psychiatric impairment can occur as the result of taking even small amounts of dissociative anesthetics. Most chronic users will undergo an unpleasant experience at least once when using a drug in this category. Chronic psychiatric impairment is not uncommon among heavy and/or frequent users as well. This is particularly true of adolescents and others with immature brains and psychological vulnerability, such as individuals with *latent* (as yet unknown or visible) psychotic tendencies. The potential for behavioral toxicity is very high due to the high degree of disorientation, confusion and impaired judgment associated with using dissociative anesthetics.

Drug in this category include:

- PCP
- Ketamine
- Dextromethorphan

### PCP (phencyclidine)

PCP is a schedule I substance that was initially developed as an intravenous anesthetic for humans. However, its bizarre side effects made it impractical for that purpose. For more than two decades, it was employed as a veterinary anesthetic and immobilizing agent, but is longer manufactured legally in the United States. However, PCP is relatively easy and inexpensive to manufacture, and so it is easily available on the street in a number of forms:

- A powdered form (angel dust, dummy dust, dust, THC/TIC/TAC, horse [elephant, pig, etc.], tranquilizer, rocket fuel, brain eraser)
- A liquid (water, embalming fluid<sup>17</sup>)
- Individual cigarettes made of marijuana, tobacco, parsley or mint leaves and treated with either powdered or liquid PCP (dips, sherms, wicki sticks, happy sticks, joy sticks, mint leaves, etc.).

PCP powder can be fine and crystalline, or a sticky substance similar in appearance to paste. It can be white, off-white, yellowish, tan or brown. Occasionally, it has a chemical or a fishy odor, the latter believed by some pharmacologists and users to be a badly synthesized product with toxic properties.

The threshold dose (ED) is approximately 1-2 mg. The “*line dose*” (the dose above which the user’s primary senses [vision, hearing, touch] begin to become unreliable) is 3-5 mg. Doses above 5 mg often result in disorientation, confusion, and psychotic behavior. To put these amounts in perspective, recall that a package of Sweet ‘n’ Low or Equal is one gram (1,000 mg.)

With oral doses, the first effects of PCP are felt at 20-30 minutes, and persist for 4-6 hours. Both intranasally administered and smoked PCP produce an onset of 5-10 minutes, and a duration of the same length as orally-administered doses. However, there is often a lingering aftereffect consisting of confusion, difficulty with memory or communication, and low to moderate dissociation that can last a day or more. Chronic PCP users may develop persistent problems, up to and including psychosis.

Videos of persons under the influence of PCP may be found at:

- <http://www.youtube.com/watch?v=AHbU8GkLTcA>,
- <http://www.youtube.com/watch?v=dDBofgWP5fM>

---

<sup>17</sup> For years, drugs called “embalming fluid” were actually liquid PCP, but recently, formaldehyde and other chemicals used to preserve human and animal remains have appeared, along with PCP, in “embalming fluid.”

- <http://www.youtube.com/watch?v=RL7p8xPp5O0>.

### Ketamine

Ketamine (Special K, Vitamin K, and K) is a schedule III substance which is used medically as an intravenous anesthetic (Ketalar). The pharmaceutical version of this drug is an injectable liquid, although ketamine in the form of a white powder is more likely to be encountered on the street.

Ketamine is similar in its effect to PCP, but is somewhat less likely to produce psychosis, panic, anxiety and/or aggressiveness. It is also a short-acting drug, with a duration of 30 to 60 minutes. After effects, when they occur, can last several hours.

Typical doses of ketamine are in the range of 1560 mg (snorted), depending on the purity of the drug and the experience that the user is seeking. The line dose is between 60 and 125 mg.

There is an expression for a particularly intense and often unpleasant ketamine experience: being in a “K hole.” This experience has been described in this manner:

*The user becomes trapped in state of detachment from their physical presence; the user can think about moving their arm, and will then see an arm moving in front of them, but the link between the thought and the moving arm does not register. The senses also become distorted, objects appear to move closer or further away resulting in the user's sight becoming fixed to one point, fearing looking away from that point as the distortions are disorientating and in the worst cases can cause nausea. The combination of these effects leave the user feeling trapped in a frozen state, as if stuck in a hole peering out; hence the expression “k-hole.”<sup>18</sup>*

### Dextromethorphan

Have you noticed that certain cough and cold medications have been taken off the pharmacy shelves and put behind the counter? This is because they either contain pseudoephedrine (which can be used to make methamphetamine) or dextromethorphan (“DXM”, “skittles”, “Tussin”). However, both of these drugs are available in Illinois and most other States without a prescription. In some areas, state or local laws may limit the amount of DXM-containing medicines that can be purchased at one time, or require the purchaser to show identification and sign a purchase log.

Two of the medicines that contain DXM are Coricidin Cough and Cold (“3-C”, “triple C”) and Robitussin DM (the source for the expression “robo-tripping”). At low doses, DXM is a cough suppressant and mild sedative, but at higher doses, acts like a dissociative anesthetic. Users describe levels of intoxication or “plateaus.” This is how one person describes these different levels:

DXM has notably different effects at different dosage levels. Users describe four distinct levels, called "plateaus". Most recreational use happens during the first and second

---

<sup>18</sup> Source: [www.urbandictionary.com/define.php?term=k-hole](http://www.urbandictionary.com/define.php?term=k-hole)

plateau. In the third and fourth plateaus, the risk of severe disorientation, confusion, anxiety and depression rises significantly. At doses that produce a “fourth plateau” experience, serious physical toxicity (as described in the section on PCP) becomes more likely.

In conclusion, there are many potential dangers associated with the use of dissociative anesthetics. Although the addiction potential of this group of drugs is moderate at best, both physical toxicity (up to and including death) and psychiatric impairment are possible outcomes of use. Interestingly enough, even people who admittedly and proudly proclaim their use of marijuana, cocaine and other drugs on the Internet have serious concerns about PCP, ketamine and DXM.

### References

- Brick, J; Erickson, CK (1998). Drugs, the Brain and Behavior. New York: Hawthorn Medical Press.
- Carroll, M.E. & Comer, S.D. (1994). *Phencycline and the Hallucinogens*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.
- Cooper, JR; Bloom, FE; Roth, RH (2003). The Biochemical Basis of Neuropharmacology. New York: Oxford Press.
- Erickson, CK (2007). The Science of Addiction: From Neurobiology to Treatment. New York: WW. Norton
- Giannini, A. James, et. al. (1993). "Behavioral Response to Buspirone in Cocaine and Phencyclidine Withdrawal," *Journal of Substance Abuse Treatment*, 10.
- Goldestein, A. (2001). Addiction: From Biology to Drug Policy (2<sup>nd</sup> Ed). New York: Oxford University Press.
- Hardman, JG & Limbird, LE (Eds) (2001). Goodman & Gilman's Pharmacological Basis of Therapeutics-10<sup>th</sup> Edition. Columbus, OH: McGraw-Hill.
- Howard, Judy, et. al. (1990). "Adaptive Behavior in Recovering Female Phencyclidine/ Polysubstance Abusers," in Spencer, John W. & Boren, John J. (Eds.), Residual Effects of Abused Drugs on Behavior, National Institute on Drug Abuse Research Monograph Number 101, Rockville, MD.
- Morgan, JP (1994). *Principles of Pharmacology and Biopharmaceutics*. In: American Society of Addiction Medicine (1994), Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine.
- Perry, David. (1975). "PCP Revisited," *PharmChem Newsletter*, Palo Alto: PharmChem.
- Petersen, Robert C. & Stillman, Richard C. (1978). "Phencyclidine: A Review," National Institute on Drug Abuse, Rockville, MD.