Introduction

Learning Objectives

The student will learn:

1. To identify when drug seeking becomes a problem.
2. What is the common link between many dependence-producing drugs?
3. To recognize the common attributes of dependence-producing drugs.
4. Identify the factors involved in drug dependence.

We are a society of drug users. If our headaches or a muscle twinges a little, we take a pill. If we are nervous, “stressed-out,” or just cannot sleep, we take a tranquilizer or sleeping pill. If we do not eat a balanced diet, we take vitamin pills, and then diet pills so we can lose the weight we gained because we were not eating a balanced diet. In fact, it almost seems that there is a pill for pretty much everything that is not “just right.” As a society we have come to depend on pills, as if the pills would correct any mistakes we make, cure any loneliness or failure we have. However, if we examine societies through the ages, we can see that our society today, is not that different, we just have a wider selection of “cure-alls.”

For many thousands of years humans have searched for ways to modify or alter their feeling of well-being and consciousness. We have sought to increase our awareness, decrease boredom, increase alertness, physical prowess, stimulate creativity, or enhance our senses. Throughout the ages we have used potions, plants, extracts, tonics, pills, and injections. All were used to achieve an altered state of consciousness. While there are many ways to achieve this altered state of reality, over the centuries man has chosen to use psychoactive drugs.

Most of the psychoactive drugs consumed were done so by personal choice, rather than professional advice. While society today does not generally approve of this unauthorized use of mind-altering drugs, this has
Introduction

not always been the case. Many of the drugs of abuse have had a very colorful history and have often been used not only for their ability to alter perception, but also to gain political, economic, and religious control over a given population.

ORGANIZATION

The first two chapters of this book lay the groundwork or background information for the drugs that will be covered. In this chapter we begin our studies on drug abuse with a brief historical perspective and an introduction to the attitude of society today toward most addictions. We will define the processes that are related to forming an addiction, and define terms that we will be using throughout this book.

Chapter 2 describes the basic steps in the synthesis and metabolism of the neurotransmitters that are primarily involved in producing the effects of a drug. The receptors of these neurotransmitters will also be considered as a potential site to enhance or inhibit drug effects. In Chapters 3–11, the different categories of drugs are examined in regard to their mechanism of action and their clinical and nonclinical usage. The final chapter examines treatment programs and the success and failures of these programs.

The primary focus throughout this book is the mechanisms by which abused drugs exert their effects on both the central and peripheral nervous system. We will examine how tolerance and dependence, both physical and psychological, develop.

OPIUM, MORPHINE, AND HEROIN

Opium has a long and colorful history. Opium is an extract of the opium poppy, and the first recorded use of opium was in Assyria, dating back to...
to the seventh century BC. However, records were also found in Samaria, now called Iran, in the year 4000 BC describing the harvest and production of opium. It was harvested and the opium extracted from the poppy seed in much the same way as it is today. The use of opium was also much the same as today, namely, reduction of pain and diarrhea, and the altered mental state of euphoria and sedation was often considered an extra benefit. Because opium was so potent, both the rulers and the holy men used opium to exert control over society.

Opium is referred to in the Iliad, where Helen of Troy mixed a potion of “freedom from grief and pain,” and everyone from Hippocrates to Galen described its various uses. During the Dark Ages, around 1000 AD, the use of opium was described in the Arab world. The Arabs then took opium to China in the ninth century and later China imported opium from India. The Chinese initially used opium to treat dysentery. Somewhat later the East India Company imported opium from China, taking it to Portugal. This use was not for the treatment of any disease.

By the seventeenth century opium was a common ingredient in many potions throughout Europe, but there were so many ingredients in these potions that very little harm was caused to the patient because of the opium content. Around the turn of the eighteenth century, the medical profession became concerned with the lavish use of opium. They were largely ignored, as most people saw no great harm coming from its use. In 1800, a German pharmacist isolated a pure alkaloid base from opium and published a paper describing the compound. This paper was completely ignored by the professional community. Twenty years later he published the same paper, only this time he called the substance morphine, the god of sleep and the paper received a lot of attention.

During the seventeenth century, all medicines were taken orally since intravenous injections were very difficult. In 1656 Christopher Wren introduced the hypodermic needle. This was not as much of an improvement as you might think as the needle had a blunt end. To use the hypodermic needle, an incision had to be made in the skin before the needle could be introduced. Surprisingly, it took many years before a bevel was added to the needle, making it possible to insert the needle without cutting the skin first. However, the introduction of the hypodermic needle and syringe added a whole new dimension to the use of opium.

Economics soon became the primary concern in the Opium Wars beginning in Europe. The British were producing opium in India, to sell to the Chinese in exchange for tea. During the American Civil War, opium or a derivative and a hypodermic needle were given to soldiers to alleviate the pain of injuries obtained during battle. Morphine was so widely used that the addiction to morphine was called the “soldier’s disease,” but was considered preferable to alcohol, as the soldiers were quieter after using morphine. Morphine was now so readily available that it was used to treat any and all painful states.
By the nineteenth century morphine was added to many over-the-counter remedies. It was used to cure alcoholics of their drinking habit and was very popular. McMunn’s Elixir of Opium and Mrs. Winslow’s Soothing Syrup were the most popular, containing heroin, opium, cocaine, and some alcohol. Mrs. Winslow’s Soothing Syrup was used to stop crying, pain from teething, and any small cough that occurred in infants. Children were dying from the overuse of Mrs. Winslow’s syrup by young, overprotective mothers.

By the 1900s, opium, heroine, and morphine were so commonly used that a very nice leather pouch could be purchased at Macy’s Department Store containing, a vial of heroin, a vial of cocaine, and a reusable hypodermic needle. These kits were well advertised in newspapers and magazines, and at the time, the use of these drugs was well accepted by society.

In 1914, spurred on by the overuse of Mrs. Winslow’s Soothing Syrup, the Pure Food and Drug Act and the Harrison Narcotics Act were passed. These two Acts eliminated the over-the-counter sale of narcotics in any form. Of course the passing of these laws made way for the illegal sale of drugs throughout the country.

This brings us to the twentieth century, where drug abuse is no longer accepted by society, and various ways to stop drug abuse where funded by the government, namely, treatment, intervention, and prevention (“just say NO”). Treatment centers sprung up around the country, primarily on the East coast where heroin addiction was being treated with the replacement drug, methadone. The different interventions were an attempt to bring the heroin addict under control. The goal was to protect society from the drug addict, not to produce a drug-free addict.

The Vietnam War saw a new type of addict, who were well educated and well off. When they returned from Vietnam, these addicts quickly overcame their drug “habit”; the demonstrators who remained in the United States were the new and more affluent drug users. This group was more against the direction of our society than the previous drug users, who were escaping pain, disease, or a very hard life. There was a resurgence in heroin use during the 1980s and 1990s and because it was a very lucrative market, Colombian drug lords added heroin to their already lucrative trade in cocaine. Mexican brown and Mexican black tar heroin flooded the market, and as the money increased, other countries, that is, the Golden Triangle in Asia, and Afghanistan also started smuggling heroin into the country. According to the 2003 National Survey on Drug Use and Health, almost four million Americans were using heroin, and the demographics show that new users are younger and coming from more affluent communities. Unfortunately, in 2013, there is again a rise in heroin use among the young educated people in our society.
AMPHETAMINES AND COCAINE

The coca leaf is the natural source of cocaine. It has been in use by the Incas in the Andes Mountains of South America since the eleventh or twelfth century. The coca leaf was controlled by the ruling class and valued far more than gold. Natives used the leaf so they could work in the mountains and not feel pain or tiredness.

During the 1800s cocaine was introduced into Europe. Dr. Sigmund Freud used cocaine on his patients and his good friend Dr. Koller, an ophthalmologist, demonstrated its anesthetic properties and used it in his practice for ophthalmic surgery. An Italian, Mr. Mariani, added coca leaves to red wine, and called it Vin Mariani. It was advertised as a wine to lift one’s mood, energy, and spirit. Vin Mariani was thought so highly of that Mr. Mariani received letters of commendation from numerous famous people, one even from the Pope, praising his wine as a gift to humanity.

Cocaine use was more restricted to affluent society because of the cost. However, with the introduction of “crack cocaine” or the free base, it became cheap and easily obtained by anyone. The 1980s were a time when stimulant abuse was increasing and the introduction of a cheap stimulant, that is, crack cocaine, produced a major change in the demographics of the drug culture that could not have been predicted.

Amphetamine, although first synthesized in the late 1800s was not extensively used until World War II. Soldiers on both sides were routinely given amphetamine to fight battle fatigue and increase endurance and outlook. Amphetamine and analogs of amphetamine became popular after the war as a tool to fight weight gain, and are still used for that purpose today. However, a more serious epidemic developed from the use of methamphetamine and methylene-dioxy-methamphetamine (MDMA or Ecstasy).

LYSERGIC ACID DIETHYLAMIDE AND OTHER HALLUCINOGENS

Hallucinogens are drugs that severely distort a person’s sense of reality. The psychedelic drugs originally used came from plants, primarily members of the nightshade family or from mushrooms, such as peyote. As early as 1500 BC, tribal medicine men referred to the use of henbane or mandrake root as a means to alleviate pain, act as a poison, or produce hallucinations leading to some type of prophecy.

An additional psychedelic comes from ergot, a naturally occurring purple fungus that comes from mold and grows on rye or wheat. This was quite common during the Middle Ages, and was not uncommon for individual farmers or whole villages to go seemingly mad. An exaggerated
6 Introduction

Figure 1.2 An exaggerated cartoon of a farmer during the Middle Ages afflicted with ergot poisoning.

cartoon of a farmer in the Middle Ages afflicted with ergot poisoning can be found in Fig. 1.2. Ergot poisoning does not just produce a “daffy” horse in the field, it occurs most commonly in contaminated grain used for cereal, and is occasionally found even today. This ergot poisoning was given the name “St. Anthony’s Fire” and the cure for this “insanity” was to make a pilgrimage to a particular shrine in France. This pilgrimage did in fact cure the affliction, as the mold did not grow in that region of France. The symptoms of this disease are pronounced mental disturbance and a severe vasoconstriction, which is very painful and can lead to gangrene. There has also been speculation that ergot poisoning may have been responsible for the Salem Witch Trials in the seventeenth century; however, there is very little evidence to support this idea.

Ergot mold is the natural form of lysergic acid diethylamide (LSD). Albert Hoffmann was a chemist working for Sandoz Laboratories in Switzerland. In 1943 he synthesized a compound called LSD-25 that he hoped would be an aid to patients with respiratory and/or circulatory problems. In fact LSD-25 is the most potent mood-altering hallucinogen known to man. LSD permeated the culture of the 1960s, from the universities to the music. Hoffmann later wrote about LSD in a book entitled “My Problem Child.”

MARIJUANA

The use of cannabis has been recorded for thousands of years. In the year 2737 BC the emperor of China wrote that there were many medicinal uses
Introduction

Figure 1.3 Marijuana leaf.

Marijuana was used in India around 1500 BC as a means to promote good health and also as a means for becoming closer to God. Its use reached Eastern Europe by approximately 500 BC where the burning plant smoke was inhaled in small tents to promote “joy.” Most often however, the Marijuana or hemp was most highly prized as a source of fiber, edible seeds, and as a medicine.

Marijuana (hemp) was grown in America in the 1700s by the founding fathers. This was to establish a textile and rope industry in the newly formed country. It is difficult to say whether any of the founding fathers smoked the marijuana leaf, as there is no recorded documentation.

If mind-altering drugs have been around for such a long time and have even enjoyed a certain degree of acceptance by society, why is drug use so frowned upon today? The effects of drug addiction on society and the individual will be discussed briefly in this chapter. We will then cover the transmitters that are involved in drug addiction and the effects of the different drugs on the central and peripheral nervous system. These two chapters provide the groundwork for our studies of abused drugs.
SOCIETY’S ATTITUDE TOWARD DRUG USE

Why is drug use so frowned upon today? The answer is unfortunately very pragmatic. Very often the primary interest is one of cost-benefit.

Drug abuse poses a cost to society and the cost is thought to outweigh the benefit to the individual.

The reasons why a particular drug constitutes a problem to society are complex. The drug and its pharmacological activity are only a starting point. If we consider the three most commonly used nontherapeutic drugs, they are as follows.

Caffeine, Nicotine, and Alcohol

Society certainly views drug addiction very differently from other forms of addiction, for example, Monday Night Football, sex, over eating and even coffee, these addictions are not viewed as negatively as drug addiction. Nicotine was once widely accepted; however, it is now viewed very negatively. Alcohol produces a mixed response. It is accepted, in fact, almost expected of one to drink socially; however, if one loses control, then it is viewed very negatively.

The drugs of abuse, both prescription and illegal drugs, form a heterogeneous group pharmacologically. One primary link is that the drug user finds the effect of the drug pleasurable and wants to repeat or sustain the effect or feelings produced by the drug.

This pleasure-seeking effect becomes a problem when the following happens.

1. Drug seeking dominates one’s lifestyle.
2. Use of the drug prevents a person from living a lifestyle that society can accept.
3. The desire or craving for the drug begins to dominate the person’s life.
4. The “habit” causes actual harm to the individual or community.

One common link of many of the dependence-producing drugs is that of ACTIVATING the mesolimbic dopamine system. When dopamine (DA) receptors are activated, this initiates a complex chain of events in the signal transduction pathway. The common link or response to the various types of psychoactive drugs is that they produce an effect, which we will call rewarding or pleasurable. These same drugs can be tested in the laboratory to determine the effect on an animal’s behavior. Animals will self-administer most of the dependence-producing drugs. The effect of the drug is said to have a reinforcing property. This means that whatever behavior the animal was performing at the time the drug was delivered, the probability of its occurring again will increase, thus causing the drug
to be administered again. In humans, there is the initial period of drug exposure, or conditioning, before a dependency is formed. The rewarding property of the drug, combined with repeated exposure, usually produces dependence. At this point, taking the drug is now the reward; not being allowed to take the drug is a punishment or a negative reinforcement.

The intensity of the withdrawal syndrome, when the drug is removed, varies depending on the class of drugs. Now drug-seeking behavior is more likely sustained because of the psychological dependence, rather than the severity of the physical withdrawal symptoms.

We should first begin by defining the terms we will be using. Drug dependence describes the state when drug taking becomes compulsive, taking precedence over other needs.

Drug addiction (an older term) implies a state of physical dependence. Physical dependence is used to describe the response of the body, when a drug is eliminated. There is a characteristic withdrawal syndrome, suggesting that the person is dependent on the drug.

Psychological dependence refers to a behavioral dependence; this dependence is characterized by a high degree of relapse and continued craving for the drug after termination of use.

Tolerance is a decrease in the pharmacological effect of a drug, upon repeated administration of the drug. Thus, it will take a greater amount of the drug to produce the same effect.

A common feature of these various types of drugs (psychoactive drugs) is that they produce dependence. Dependence is produced primarily because there is a rewarding or positive effect from the drug.

**Dependence**

The term positive reinforcement is used to define the repeated occurrence of a response after administration of a drug. If after repeated administration of a drug, the drug is removed or no longer administered, then removal of the drug constitutes a negative reinforcement.

The physical withdrawal syndrome, which is associated with the state of physical dependence, is one manifestation of addiction. The intensity of the physical withdrawal symptoms varies and is particularly pronounced in the case of opioid withdrawal.

Lastly, conditioning also plays a role in sustaining drug dependence. If we consider heroin or nicotine, in the case of these drugs, environment plays an important role. The sight of the syringe or a cigarette, a smell, a coffee shop, or even a particular person, anything can become associated with the pleasurable experience of the drug, such that the stimulus (i.e. the cigarette, person or place etc.) evokes the response or craving. This was demonstrated many years ago in the experiment Pavlov performed using a conditioned stimulus, that is, a bell. When a hungry dog smelled food, it began to salivate. If a bell was rung every time the dog was fed,
the bell soon became associated with food. Finally, the sound of the bell alone produced salivation.

**Reward Pathways**

An important reward pathway involved in the formation of drug dependence is the mesolimbic dopaminergic pathway. DA coming from the ventral midbrain (A10 cell group) projects to the nucleus accumbens and limbic region. This pathway constitutes a reward pathway.

All of the drugs that we will discuss produce dependence. This includes the opioids, marijuana, amphetamines, and cocaine. All of these drugs produce an INCREASE in the release of DA. This initiates a complex chain of events in the signal transduction pathway for the neurotransmitter DA. Chronic treatment with drugs like opioids or cocaine increases the amount of adenylate cyclase and other components in the signaling pathway including G proteins. Increases in cAMP, produces changes in cell function through a cAMP-dependent protein kinase, which controls ion channels.

**Summary**

The factors involved in drug dependence:

1. The psychoactive drugs produce an effect that is pleasurable and could be defined as a reward.
2. Continued use produces a dependency such that withdrawal of the drug produces a physical withdrawal syndrome.
3. The psychological dependence can last far longer than the physical dependence.

To summarize the important facts:

1. Dependence develops after multiple uses of a psychoactive drug.
2. The psychoactive drugs that produce dependence are varied and act through a variety of different neurochemical mechanisms.
3. The common attribute of all of these dependence-producing drugs is that they produce a feeling of euphoria or act as a “reward” which makes one feel good.

Common attributes of dependence-producing drugs:

1. A tolerance develops.
2. The withdrawal syndrome occurs, to a greater or lesser degree, if the drug is removed.
3. A strong psychological dependence is also formed, which is associated with subtle cues or stimuli.
4. The psychological dependence is long lasting and can lead to relapse.

**Review Questions**

1. Is there a relationship between physical dependence and tolerance?
2. How does a drug act as a positive reinforcer?
3. Why does society view addiction so negatively?

**REFERENCES AND ADDITIONAL READING**
