Psychopharmacology

R.H. Ettinger

Chapter 2: Psychopharmacology: Pharmacokinetics and Pharmacodynamics

Have you ever wondered whether getting that morning coffee might work just a little bit better if you could hook yourself up to an iv? While being tied to a drip bag with a long thin tube might get caffeine into your blood stream much more quickly, missing out on the sensory aspects of this morning ritual would make your experience much less pleasant. As we will see in this chapter the action of a drug can, and often does, depend not only on its pharmacological properties, but on how rapidly it enters the brain, the context in which it is administered, and our expectations of its effects. We begin by examining how routes of administration and drug dose affect how much and for how long drugs are available at target sites. We will also explore how repeated exposure to a drug alters its effectiveness. These are all topics of **pharmacokinetics**, the science of how drugs are absorbed, distributed to body tissues, and eliminated from the body after metabolism.

Drug Names

Before we discuss pharmacokinetics, however, a brief discussion of the drug naming convention is in order. Students are often appropriately confused over drug names as most drugs have several. For example, drugs can be named after their chemical structure which may be useful to a chemist, but these names are far too awkward to use in any other context. The **chemical name** for the popular antidepressant Prozac is *N*-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]-propan-1-amine. A drug's chemical

name reveals its chemical composition and molecular structure. Pharmaceutical companies may also patent **brand names** or trade names for their product. These brand names reveal little if anything about the drug's makeup or structure. Most of us are familiar with drug brand names because these are the names that are used in advertising the drug. When drugs are marketed in different countries they may have several brand names. The name Prozac is a brand or trade name. Pharmaceutical companies typically receive exclusive rights to manufacture and distribute brand name drugs that they have developed. Once this exclusivity has expired (typically after 5 to 7 years) a drug can be manufactured and distributed by other drug manufactures as a **generic drug**. The generic drug name can be used by any number of companies who market and distribute the same generic drug. The generic name for Prozac is fluoxetine. Generic drugs must contain the same active ingredients as the original brand name drug and they must be pharmacologically equivalent. Because several manufactures may compete to produce and market generic drugs their cost is often considerably less than their equivalent brand named drug.

Chemical Name	Brand (trade) Name	Generic Name
N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]-propan-1-amine	Prozac	fluoxetine
methyl alpha-phenyl-2-piperidineacetate	Ritalin	methylphenidate
N,N,*6-trimethyl-2-(4-methylphenyl)-imidazo(1,2-*a*)pyridine-3-acetamide*	Ambien	zolpidem
7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one	Valium	diazepam
4, 5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one	Percoset, Percodan	oxycodone

Table 1: *Examples of several common drug names. Note that the drug brand name is always capitalized while the generic name is not.*

Pharmacokinetics: Drug Absorption, Metabolism, and Tolerance

Drug Absorption refers to the mechanisms by which drugs get into the blood stream and distributed throughout the body. Because our focus in this text is on psychopharmacology we are particularly interested in how drugs get into the brain. How quickly and how much of a drug reaches the brain depends on several factors including how it is administered and how readily molecules of the drug pass from the blood stream into neural tissues. We first examine routes of administration and then we will look at factors that influence a drugs passage from blood into the brain.

Oral Administration (po) Perhaps the most common route of drug administration is the ingestion of a pill or tablet, but it would also include the oral ingestion of liquids. If taken orally a drug must be both soluble in gastric fluids and not destroyed or broken down by them so it can cross from the lining of the stomach and upper intestine into the

blood stream. In order to pass through the tissues lining the gastric tract a drug must also be fat soluble to some extent. The greater its solubility in fat the more rapidly it can permeate the mucosal lining into the blood. Fat solubility will also be a factor in determining how rapidly a drug can pass from the blood stream into neural tissues in the brain. The reason fat solubility is important is that the tissues lining the stomach, the upper intestine, blood vessels, and neurons are composed primarily of fats or lipids. Fat soluble compounds literally dissolve in these tissues and pass through by diffusion. Oral ingestion of drugs is often the most preferred method of administration but absorption may take between 1/2 to 3 hours depending on a drug's fat solubility and where it is absorbed. For instance, some drugs are designed to quickly dissolve in the mouth and are absorbed through the mucosal lining in the mouth and throat. Other drugs are more slowly absorbed in the lining of the upper intestine. Most of us are familiar with how long it takes an oral analgesic to relieve the pain associated with an extracted tooth. When a drug may not be stable in stomach acids and enzymes, or when it needs to reach the brain more quickly, other methods may be preferred.

Inhalation A number of both illicit and legal drugs are typically administered by inhalation including nicotine and marijuana. This method is preferred for drugs of abuse because they are absorbed quickly through the lungs into the blood stream. The lungs have a very large surface area and blood volume so absorption will take a mere few seconds. Drugs used to administer anesthesia (e.g., halothane) are often administered by inhalation. The level of anesthesia is then carefully monitored and regulated throughout its duration. For drugs used to treat psychological disorders inhalation is not preferred because therapeutic doses of these drugs require a stable blood level unlike the rapid

spike in levels preferred by drug users. Most of us are familiar with a variety of bronchial and nasal inhalers used to treat asthma and congestion. Other drugs such as methamphetamine, cocaine, and heroin vaporize upon heating and these vapors are inhaled. This is often preferable to oral or nasal administration because this method produces an intense state of euphoria and it is often less risky than intravenous administration when needle sharing may spread diseases such as AIDS.

Intravenous (iv) An intravenous injection is a rapid and precise way to administer a drug. Drug absorption is rapid because it is delivered directly into venous blood where it is rapidly distributed throughout the circulatory system. Passage of the drug through membranes of the gastric system or the lungs is bypassed completely. Intravenous administration is more precise because the entire amount of the drug administered gets into the blood stream. Following oral administration unpredictable amounts of the drug get trapped temporarily in fat tissue making the amount reaching the blood difficult to determine. Because drugs administered intravenously have such rapid onset, they are also much more dangerous. Overdose by intravenous administration can easily cause death by respiratory or heart failure and severe allergic reactions. The intravenous use of recreational drugs is of particular concern because they are often administered in less than septic conditions increasing the risk of infections and diseases spread by shared needles. Additionally, drugs mixed and prepared outside of specialized laboratories often contain contaminants. The soluble contaminants may be toxic and those that are insoluble actually may lodge in the lungs and blood vessels causing damage to these and other organs.

Intramuscular (im) Drugs can also be delivered into skeletal muscle where they are absorbed more slowly. Absorption typically occurs within one hour, depending on the injection site and the amount of blood flow to the muscle tissue. Often drugs administered intramuscularly are mixed in an oil base to further slow their absorption. Several hormones are commonly administered intramuscularly including Depo Provera (medroxyprogesterone) as a female contraceptive and testosterone for hormone replacement in men.

Transdermal Nicotine patches, motion sickness patches, testosterone replacement gell, and some forms of female contraceptives are examples of transdermal drug administration. Because the skin is relatively impermeable to water soluble substances these drugs need to be fat soluble in order to pass through the skin. Absorption is quite slow and can be sustained over several days or weeks.

Subcutaneous (sc) Subcutaneous administration may consist of either a subdermal injection or the implantation of a drug in pellet form. Several hormones are available in pellet form including the newly approved female contraceptive Implanon. Implanon delivers contraceptive hormones for up to three years per implant.

Intraperitoneal (ip) The delivery of a drug directly into the abdominal cavity beneath the peritoneum is a common route of administration in small laboratory animals. This method of drug administration is not used for humans because of the risks of contaminating the abdominal cavity and possible damage to internal organs. Drugs are administered to small animals with this procedure when rapid absorption is required. You might wonder why researchers don't prefer intravenous injections in these cases since

more accurate dosing can be achieved this way. However, as you might imagine, delivering drugs intravenously in small laboratory rats and mice can be quite difficult.

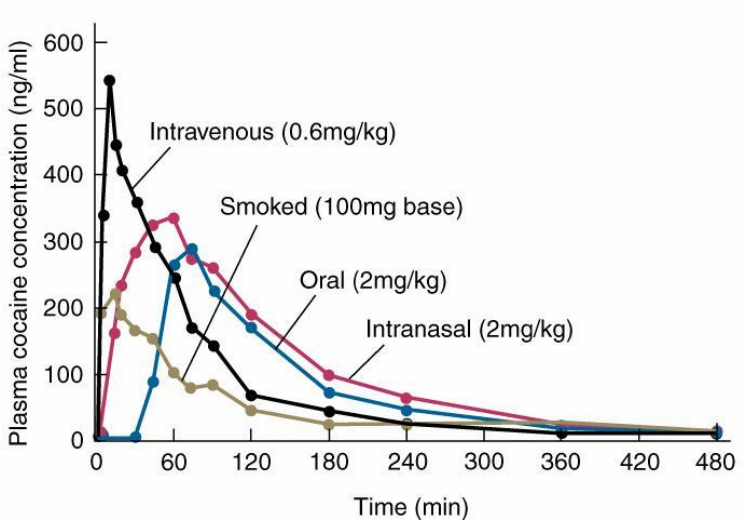

***Figure 1**: Comparison of absorption times for different administration routes. Adapted from Carlson, 2010)*

Route of Administration	Main Advantages	Main Disadvantages
Oral (po)	Patient-administration, relatively safe	Delayed and variable absorption
Inhalation	Rapid availability, patient administration, reliable absorption, accurate blood levels	Irritation of nasal passages or the throat and lungs, possibility of overdose
Intravenous (iv)	Rapid availability, reliable absorption, accurate blood levels	Patient-administration difficult, possibility of contamination and infection from needles, possibility of overdose
Intramuscular (im)	Prolonged and reliable absorption, easy to administer	Patient-administration difficult, possibility of contamination and infection from needles
Transdermal	Prolonged and reliable absorption, easy to self-administer	Local irritation, variable absorption, more difficult to regulate blood levels
Subcutaneous (sc)	Prolonged and reliable absorption, easy to administer	Patient-administration difficult, possibility of contamination and infection from needles
Intraperitoneal (ip)	This method is primarily used to administer drugs to smaller laboratory animals when intravenous administration is not feasible	Possibility of damage to internal organs, local irritation at injection site, delayed absorption compared to intravenous injection

Table 2*: Routes of drug administration*

Cell Membrane Permeability Once a drug is administered it must pass through several membranes before it actually reaches the brain. The first membranes drugs encounter are the cell membranes that make up the linings of the gastric system, skin cells, muscle and fat cells, or the mucosal lining of the lungs. All of these tissues are composed of a phospholipid bilayer made up of complex lipid (fat) molecules arranged in two rows. These phospholipid molecules are composed of a head region that is negatively charged

and an uncharged tail region that is split into two segments. These molecules are arranged such that their heads form both the inner and outer surfaces of the membrane and their tails remain in-between these charged segments. The negatively charged heads of these molecules are hydrophilic (attracted to water) are exposed to both the intra and extra cellular fluids. The uncharged tails are hydrophobic (repel water) and therefore prevent fluid and water soluble substances from easily passing through the membrane. Imbedded in this arrangement of phospholipid molecules are protein molecules that serve a variety of transport functions. In order for substances to pass through the cell membrane they must either be carried through by one of the specialized transporter molecules or be fat soluble and essentially dissolve in the membrane and pass through by diffusion.

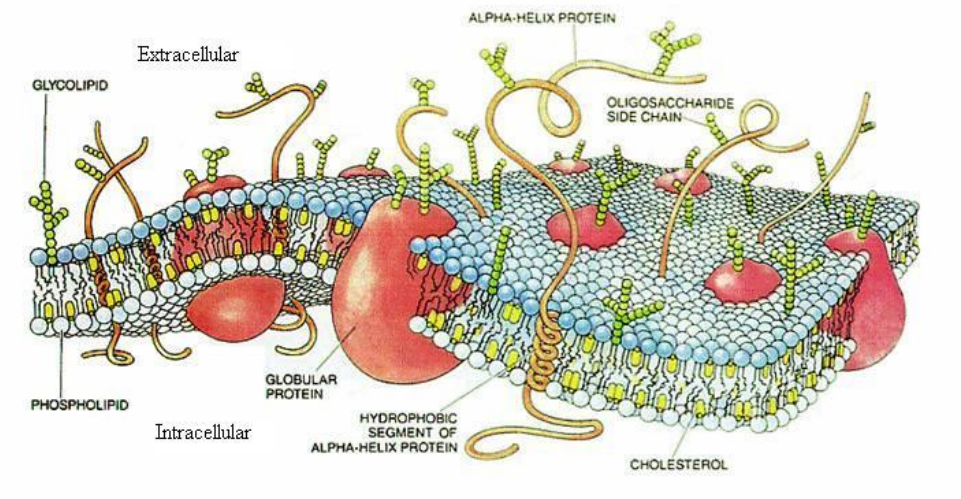

Figure 2*: Cell membrane. The arrangement of phospholipid molecules into a bilayer with negatively charged hydrophobic heads. This arrangement keeps fluids from passing through the cell membrane. Molecules may pass through the cell membrane if they are carried through by proteins imbedded in the cell membrane or if they are fat soluble and enter by diffusion.*

Substances must also pass through small blood vessels called capillaries to enter and leave the blood stream. Capillary membranes are constructed of tightly packed single layer of cells that have small gaps between them. Substances that fit through these gaps can enter and leave the blood stream by diffusion. That is, diffusion pressure forces a substance through the membrane down its concentration gradient until the concentration is essentially equal on both sides of the capillary wall. Most drugs easily pass through capillary membranes this way and become distributed throughout the body's tissues. The greater the blood flow to tissue, the greater the concentration of drug. Because the brain has relatively high blood flow, we would expect higher concentrations of drug there. However, an additional membrane must be crossed before drugs can enter the brain.

Blood Brain Barrier The capillaries that that circulate blood throughout most of the brain are constructed differently than capillaries in other tissues. Because the brain requires a very stable and protected environment to function effectively substances cannot easily pass between small gaps in the capillary membrane. These capillaries are constructed of cells with tight junctions allowing only very small molecules to pass. Additionally, the capillary walls are surrounded by a type of glial cell called an astrocyte. These astrocytic feet provide an additional barrier by tightly adhering to the capillary endothelial membrane. This impermeable construction is referred to as the **blood brain barrier (or BBB)**. Some essential substances such as glucose and some amino acids are carried through by specialized transporters in the capillary membrane. Fat soluble substances, including all psychoactive drugs, can dissolve in the membrane and pass through by diffusion. The blood brain barrier provides an effective means to protect the brain from perturbations in the chemical environment of the blood stream. Additionally,

the blood brain barrier protects the brain from potentially toxic substances including most viruses and bacteria.

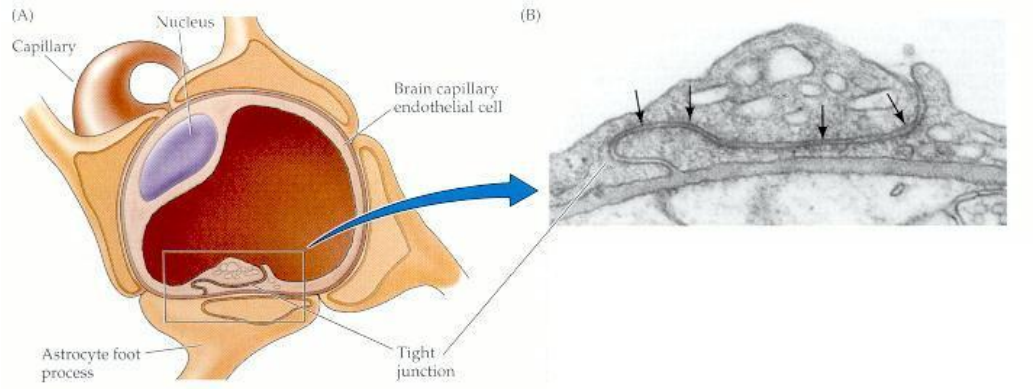

Figure 3*: Blood Brain Barrier. Tight junctions between astrocytic (glial cell) end feet and capillary endothialial cells (A). Electron micrograph showing tight junctions between capillary endothelial cells and astrocytic feet (B). Adapted from Goldstein, Goldstein, and Betz (1986).*

There are a few areas of the brain where the blood brain barrier is relatively weak allowing some substances to be detected by specialized neurons in those areas. For example, neurons in the area postrema of the medulla detect some toxic substances and it triggers vomiting to rid the body of potentially toxic substances still in the stomach. Others areas, including the sub fornical organ located on the underside of the fornix and between the lateral ventricles, has a weak blood brain barrier and detects the presence of hormones involved in the regulation of fluid balance. The blood brain barrier posses a significant obstacle to drug development. In order for drugs to reach their target receptors in the brain they must pass through the blood brain barrier.

Placental Barrier Pregnant females have an additional barrier that separates the blood system of the mother from that of the fetus. This barrier, however, must allow essential substances including nutrients and oxygen in the mother's blood to enter into the fetal

blood supply. In addition, it must allow metabolic waste produced by the fetus to be eliminated through the mother's circulatory system. The placenta is an ineffective barrier to drugs ingested by the mother and the fetus can have drug levels that are equally high. This is why it is critically important to avoid potentially harmful drugs, such as alcohol, during pregnancy. Fetuses exposed to addictive drugs such as heroin, methamphetamine, and cocaine show symptoms of withdrawal during maternal abstinence. It is important to keep in mind, however, that most drugs used to treat psychological disorders are not necessarily harmful to a developing fetus.

Drug Metabolism

Once a drug has entered the blood stream and begins to circulate throughout the body much of it is becoming attached to inactive proteins or dissolved in fat tissue and some of begins to undergo metabolism and excretion. The drug bound to inactive sites is referred to as **depot binding**. As the blood concentration of the drug begins to drop, some drug bound to depot sites reenters the bloodstream (down its concentration gradient), thereby prolonging its activity. The drug remaining in circulation begins to be excreted.

There are several ways in which drugs and their metabolites leave the body; through exhalation (breathalyzer tests for alcohol rely on this), perspiration through the skin, and they are excreted through the kidneys. Only small amounts of volatile drugs like alcohol are actually exhaled, but significant amounts are excreted through perspiration and the kidneys after metabolism. If fat soluble drugs did not undergo metabolism they would continue to be reabsorbed and released by tissues. Metabolism of foreign material by the liver is an essential mechanism to rid our body of potentially toxic substances and sometimes these substances damage it. For this reason, liver function is

routinely monitored in individuals taking certain drugs because the drug or its metabolite may be toxic. And, as you may know, the liver is often severely damaged in alcoholics.

Drug metabolism by enzymes in the liver typically results in inactive water soluble metabolites that are filtered out by the kidneys. In some cases, however, the metabolite of a drug may also be as, or even more, active than the parent drug. These active metabolites reenter the blood system and are absorbed again. Drugs that have active metabolites have significantly longer durations of action than drugs that do not. The active metabolite is eventually metabolized into inactive water soluble compounds and filtered out of the blood by the kidneys.

The kidneys are located in the back of the abdomen below the ribs. They function to filter and to excrete byproducts of metabolism and to regulate body fluids. Once a drug is metabolized by liver enzymes its water soluble metabolites are captured in the kidneys and excreted in urine. Drug testing for illicit drugs (actually their metabolites) is often conducted on urine samples. Approximately 1 liter of blood plasma is filtered by the kidneys each minute and over 99.5% of this fluid is returned into circulation. The remaining fluid is excreted as urine.

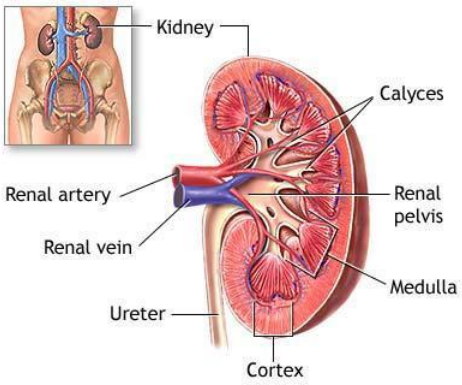

Figure 4*: Each kidney filters about 1 liter of blood each minute. Drug metabolites are excreted through the kidneys.*

Drug Half-Life As the body continues to metabolize and excrete a drug that is in circulation its concentrations in the blood and other tissues begin to decline. The time course of this decline can be accurately measured by assays of blood taken at specific intervals after drug administration. One useful measure of the time course of drug elimination is called elimination **half-life**. A drug's half-life is the amount of time it takes for a drug's initial blood level to be decreased by metabolism and elimination by 50% (1/2 of its peak level). In Figure 5 the drug reaches a peak blood plasma level of approximately 20 mg/l and is quickly redistributed to tissues over the first hour. After one hour plasma concentrations fall linearly as plasma and tissue concentrations are at equilibrium. From hour 2 to hour 5 the plasma concentrations fall by one-half (from 8 mg/l to 4 mg/l) indicating a drug half-life of 3 hours. This 3 hour half-life remains constant for this specific drug. Therefore, in the next 3 hours the plasma level will be decreased by another 50%, or down to 2 mg/l, and to 1 mg/l after 11 hours or 3 half-lives. Different drugs have different half-lives ranging from hours to days. For example, cocaine has a half-life of about 1 hour. The popular antidepressant Prozac has a half-life of about 48 hours, but it has an active metabolite that has a half-life of almost 6 days. Because of its relatively long half-life, missing a daily dose may not be problematic.

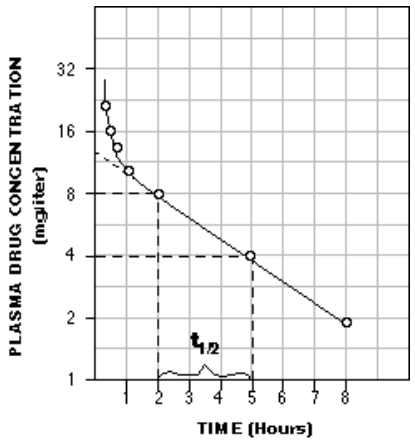

Figure 5*: Drug Half-Life. Plasma concentrations of a drug following an intravenous injection. Concentrations were measured every 15 minutes following administration for the first hour, then at hour 1, hour 5, and hour 8. During the first hour plasma concentrations fall rapidly as the drug was redistributed to tissues. After 1 hour the plasma concentration is essentially equal to tissue concentrations and levels fall in a linear manner. In this example the half-life ($t_{1/2}$) is 3 hours.*

The concept of elimination half-life is important for several reasons. First, knowing a drug's half-life will allow us to predict its duration of action. And, knowledge of a drug's half-life allows for adjusting dose intervals to achieve a steady blood level of the drug. Drugs used to treat most conditions; including psychological disorders and pain are most effective when blood levels fall within a narrow range. When blood levels fall below this range the drug response is too low to be effective. When its level is above this level it may be toxic or lethal.

This relationship, between a drug dose and it physiological effects, is called a **dose response curve**. As shown in the figure, there is little physiological response until the dose is increased. Then, as the dose continues to increase there is a sharp rise in its effectiveness until a point at which no further increase in effectiveness is produced. When examining the effectiveness of oxycodone on pain for instance, we see that below doses

of 0.01 ug/ml of blood there is little relief from pain. Above 0.01 to about 0.10 ug/ml there is a sharp rise in analgesia. Above doses of 0.10 ug/ml the analgesic response is essentially flat. Most drugs produce several physiological effects and this is certainly true for the opiates like Oxycodone. In addition to analgesia we can observe its effects on respiration. At low therapeutic doses there is little **respiratory depression** (decrease in respiratory rate). At doses approaching 3.0 ug/ml respiratory depression begins to become a concern. And, at blood levels over 4.0 ug/ml the drug may be lethal--producing complete respiratory depression. This discussion reveals that drugs may have several dose response curves, one for each physiological response. Furthermore, these dose response curves may not overlap. Next we examine how repeated exposure to a drug can actually shift a dose response curve.

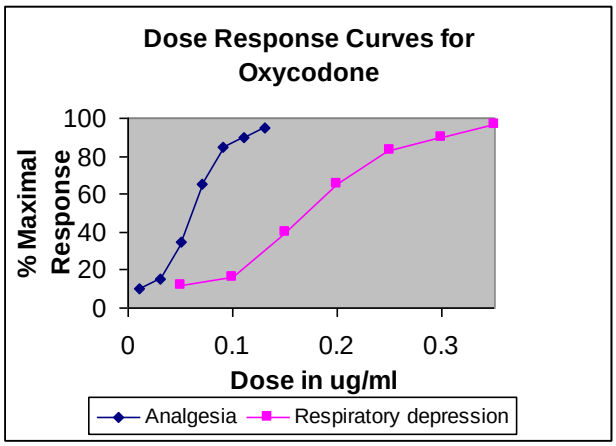

***Figure 6**: Dose response curves for oxycodone. The dose response curve for analgesia rises rapidly from about 0.01 through 0.05 ug/ml. After about 0.10 ug/ml there is little increase in analgesia. The dose response curve for respiratory depression, however, rises gradually from about 0.05 ug/ml through doses of 0.25 ug/ml. At doses exceeding 0.30 ug/ml respiratory depression is almost certain.*

Tolerance

As implied above, dose response curves are not static. After repeated administration the effectiveness of a dose of the analgesic oxycodone, for example, diminishes considerably. The decrease in effectiveness of a dose of drug (a shift to the right in the dose response curve) following repeated administration is called **tolerance**. Tolerance occurs to all drugs taken over a period of time but it occurs most rapidly to drugs in the opiate family (oxycodone and morphine are opiates). In fact, when an individual experiences tolerance to oxycodone that person will also be tolerant to other opiates including morphine. This phenomenon is called **cross-tolerance**.

There are a variety of mechanisms that contribute to drug tolerance and it appears that some mechanisms contribute to tolerance to a greater extent than others for different classes of drugs. For this reason, tolerance may develop at quite different rates to different drugs. In some cases tolerance can develop over the course of a week and in other cases it may take many months or even years. Furthermore, some changes in drug responsiveness that contribute to tolerance are easily reversed when the drug is discontinued while other mechanisms may persist long after. We know the most about tolerance to drugs in the opiate and stimulant families since these families of drugs have been studied most extensively.

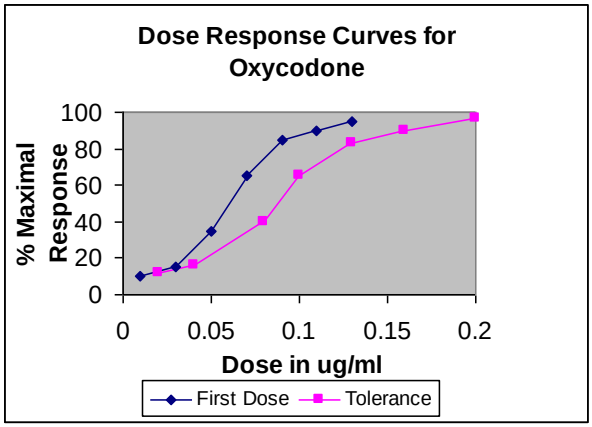

***Figure 7**: Tolerance to the analgesic effects of oxycodone is expressed as a shift in the dose response curve for analgesia to the right.*

Metabolic Tolerance As we discussed above, psychoactive drugs must undergo metabolism by enzymes in the liver before they can be excreted. The enzymes responsible for the metabolic enzymes that break drugs into water soluble compounds actually increase in availability after repeated exposure to a drug. This results in more rapid metabolism as more enzymes are available for degradation. For example, alcohol is metabolized by the liver enzyme alcohol dehydrogenase which catalyzes the oxidation of alcohol into acetylaldehyde. Acetylaldehyde is further converted into acetic acid by acetyldehyde dehydrogenase. The amounts of these liver enzymes increase with exposure to alcohol contributing to alcohol tolerance.

Cellular Tolerance In addition to enzymatic degradation, there appear to be cellular adaptations to some drugs that diminish their effects on target cells. One cellular adaptation that follows drug-induced increases in neurotransmitter availability is **downregulation**. When synaptic activity increases significantly the number of postsynaptic receptors may actually be reduced making the post synaptic cell less responsive to chemical transmission. Another mechanism of downregulation is an

increase in the sensitivity of autoreceptors on the transmitting neuron. Autoreceptors essentially function to slow down the activity of the firing cell resulting in less neurotransmitter being synthesized and released. Both mechanisms of downregulation contribute to drug tolerance.

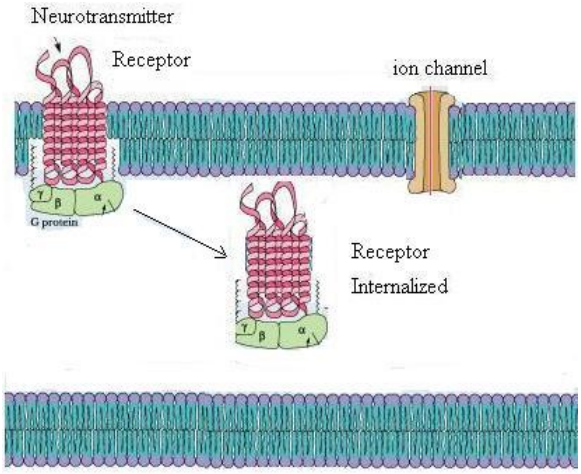

Figure 8*: Downregulation of Receptors. Metabotropic receptors may become internalized during the development of tolerance. The expression or the internalization of receptors may occur rapidly and underlie the dynamics of conditioned tolerance.*

Associative Tolerance Given what we have learned about tolerance so far it might be quite surprising to observe that an organism could display tolerance to a drug in one context, but not in another. After all, if tolerance results from downregulation and more efficient enzymatic degradation, why would the context where a drug was administered make any difference in how we respond to it? In an experiment conducted by Siegel (1975) rats were administered progressively increasing doses of morphine over a period of several weeks. At the end of this period all of the animals had developed tolerance and were receiving a dose of morphine that would be lethal to most untreated

animals. On the final day of morphine administration half of the animals received their injections in a novel context while the remaining half received their injections in the familiar drug environment. Most of the animals that received drug in the novel context demonstrated signs of overdose while none of them receiving their drug in the familiar context did. This experiment, and many that have followed, reveals that contextual cues associated with drug onset become conditioned stimuli that can elicit tolerance. When animals received their drug injection in a novel context tolerance was not expressed. In this case the conditioning is a form of Pavlovian conditioning where contextual cues (conditioned stimuli)) associated with drug onset (unconditioned stimulus) come to elicit conditioned tolerance (a conditioned response). The conditioned response in this example is called a compensatory response to the effects of the drug. Compensatory conditioned responses function to maintain relatively stable internal conditions. Tolerance compensates for the large perturbation caused by opiate administration. It is important to point out that this phenomenon is not habituation which could be defined as a decrease in the effectiveness of a stimulus (in this case a drug) to elicit a response. Since habituation is not an associative form of conditioning it would not be context specific.

In the author's laboratory we have further demonstrated that these contextual cues can undergo extinction of tolerance when animals are exposed to the drug context without drug injections. After extinction, tolerance to morphine is not expressed. Extinction can be reversed, however, when a single morphine dose is administered in the original drug context. This reinstatement of tolerance can even occur months after extinction suggesting that conditioned tolerance to drugs may never be completely

reversed. The neural mechanisms underlying associative tolerance are still unknown but rapid internalization of receptors and **downregulation** are likely to mediate it.

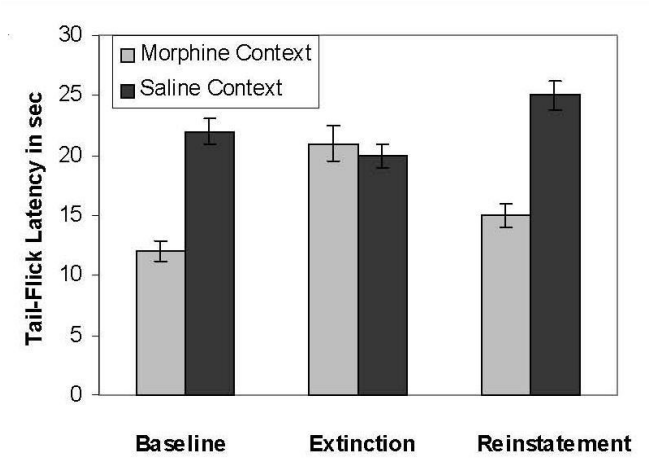

Figure 9*: Conditioned tolerance, extinction, and reinstatement. Animals administered morphine in a distinctive context show tolerance (a decrease in tail-flick latency) in that context but not in a context where saline was administered (longer tail-flick latencies). After several trials where they were exposed to the distinctive morphine context without drug administration tolerance was extinguished (longer latencies). Tolerance can be reinstated following a single exposure to the morphine context with a morphine injection. (From author's laboratory).*

Figure 10*: The distinctive context for morphine administration. (Photo from author's laboratory).*

Reinstatement of conditioned tolerance, and other drug responses, may contribute to the high recidivism rates for recovering drug addicts. After treatment, re exposure to the context where drugs were previously used may elicit drug behaviors including drug craving and withdrawal. Furthermore, rapid reinstatement of tolerance and addiction would appear following drug use after abstinence.

Behavioral Tolerance The associative tolerance described above involves conditioned associations between a context where drugs are administered and drug onset. This form of conditioning is referred to as Pavlovian conditioning and it appears to contribute to a rapid decrease in receptor availability. Operant conditioning can also contribute to drug tolerance. For example, if animals are given intoxicating doses of alcohol before learning a complex motor task they tend to perform that task better when under the influence of alcohol than in a sober state. Alcohol in this example becomes a discriminative stimulus which occasions a set of behavioral adaptations to motor behavior (Wenger et al., 1981). Behavioral adaptations such as these are referred to as behavioral tolerance or **state-dependent learning**.

Drug Toxicity and Overdose

As we can see in the dose response curves above, psychoactive drugs often have several distinct effects and not all of them are desirable. Additionally, some drug effects are caused by the pharmacological actions of the drug and others are not. For example, morphine is well known for its analgesic properties, but it also produces hypothermia, constipation, and at high doses respiratory depression. All of these side effects are attributable to is pharmacological actions. It is also possible to have non pharmacological

reactions to drugs such as an allergic reaction. Although quite rare with morphine, allergic reactions can occur with any drug and they can be lethal. Other non pharmacological reactions could include damage to the liver or kidneys where drugs are concentrated as they are responsible for drug metabolism and excretion. Certain drugs may also be harmful to a developing fetus and cause developmental abnormalities or damage to developing organs. All of these drug reactions are examples of drug toxicity which is a measure of the potentially harmful effects of a drug. Some toxic reactions may be minimized by carefully adjusting drug dosages, but others such as allergic reactions can occur with any dose.

At high doses all drugs can produce toxic reactions and even death. When a drug's toxic reactions are attributable to an excessive dose it is called an *overdose* reaction. Overdose reactions can be lethal and they are most likely attributable to respiratory, kidney, or liver failure. In experimental animals, where drug toxicity is investigated, the dose that is lethal (LD) to 50% of the animals receiving it is called the LD_{50} dose. When the dose is lethal to all of the experimental animals it is the LD_{100} dose. A drug's safety is determined by comparing the drug's therapeutically effective dose (ED) with its lethal dose. The area between these two dose response curves is called the **therapeutic index**. Typically, the wider the range or therapeutic index between a drug's effective and lethal doses, the safer it is.

As cellular and conditioned tolerance to a drug develop synaptic changes including downregulation of receptors occurs and the dose response curve shifts to the right. These changes may not occur at the same rate at all sites of drug action. As a result, tolerance to some drug effects may occur at different rates than others. If tolerance to the

therapeutic effect occurs at a faster rate than to a drug's adverse or toxic affects the therapeutic index narrows. For example, tolerance appears to occur more quickly to an opiate's analgesic effects (its ED) than to effects on respiratory centers (its LD). This contributes to the high risk of overdose observed in experienced, tolerant drug users. In Figure 11 the effective and lethal dose response curves are shown for the analgesic oxycodone. As tolerance to the analgesic effects begins to develop the dose response curves for effective and lethal doses merge, considerably increasing the risk of overdose.

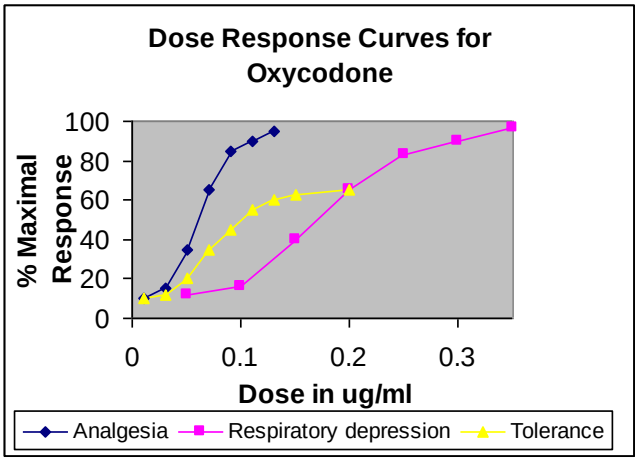

Figure 11: *As tolerance develops to oxycodone's analgesic effects the effective dose response curve moves to the right narrowing the therapeutic index.*

Placebo Effects

Not all drug effects are caused by pharmacological properties or even drug interactions with receptors. In fact, recent research on the effectiveness of antidepressant medication has confirmed that about one half of the improvement in depression symptoms can be attributed to the **placebo** effect. Just what is the placebo effect and how

can it contribute significantly to the treatment of depression and chronic pain? A placebo is a pharmacologically inert substance administered under the guise of medication. In well-designed clinical studies neither the patients nor the physician know which patient group receives the placebo or the actual medication. This **double-blind** approach is intended to rule out patient compliance as well as physician biases that may flaw the results. As shown in Figure 12 the proportion of patients who respond to treatment for depression has increased steadily over the past 20 years. While it would be tempting to say that this increase reflects improvements in antidepressant drugs over these years, how would this account for the same increase in the effectiveness of placebo treatment which contributes to the same rate of improvement? The figure also reveals that in the year 2000 about 55% of the patients treated with medication responded positively while about 30% of the patients receiving placebos improved. In other words, the placebo effect appears to account for more than 50% of the improvement in depression symptoms.

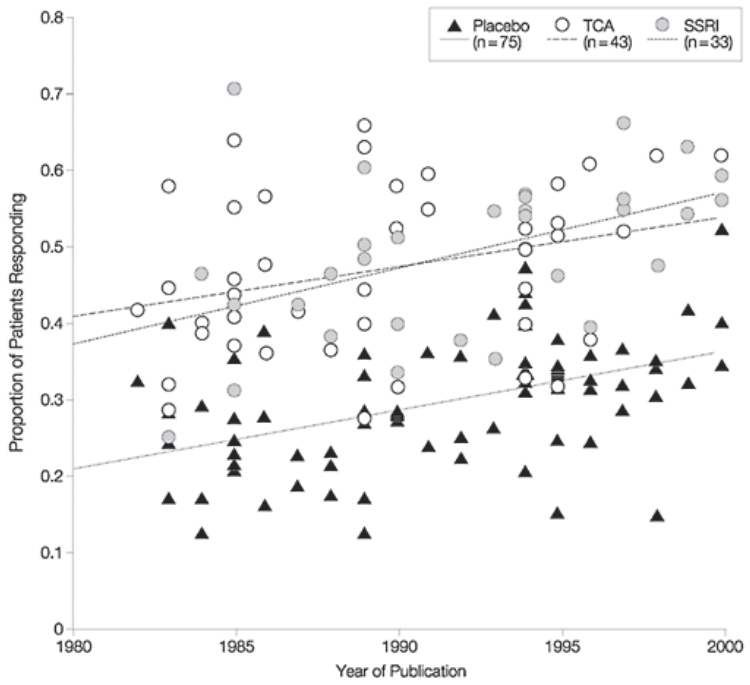

Figure 12. Proportion of patients assigned to placebo, tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs) who showed a 50% or greater improvement in Hamilton Rating Scale for depression score by year of publication. Walsh, B.T., Seidman, S.N., Sysko, R., & Gould, M. (2002).

Similar results on the effectiveness of placebos are regularly observed in comparisons of placebos with analgesics for postoperative and chronic pain. And, a number of these studies have further revealed that the placebo effect for analgesia is mediated by the endogenous opiate system (e.g., Zubieta et al., 2005). In fact, the drug naloxone, which blocks opiate activity, also blocks the placebo effect suggesting that ingesting a placebo can activate the endogenous opiate system and alleviate pain by the very same mechanisms opiate analgesics can (Levine et al., 1978). Because the neural mechanisms for pain and analgesia are well understood, this has been an ideal model to investigate the neural mechanisms of placebo effects.

Progress has also been made in revealing the mechanisms mediating the antidepressant action of placebos. While investigators have observed neural changes in the cortex of placebo treated patients, which are similar to the effects observed after antidepressant therapy, the neurochemical mechanisms for the placebo effect in the treatment of depression are still unknown (Benedetti et al., 2005). With this in mind, the placebo effect accounts for a significant amount of the treatment effect observed following drug therapy and must be taken into account in studies of drug effectiveness. Simply comparing the efficacy of drug treatment to non treated control subjects might lead to flawed conclusions about the value of drug treatment.

In this section we have examined how the effects of a drug depend how it is administered, how rapidly and completely it is absorbed and how repeated exposure and drug administration context can alter drug effectiveness by contributing to the development of tolerance. Additionally we have examined how to evaluate the safety and effectiveness of a drug by comparing dose response curves for its therapeutic and toxic effects. We have also seen that the placebo effect can contribute significantly to a drug's effects and how well designed studies can isolate this contribution. We next look at how drugs interact with receptors to produce their effects.

Pharmacodynamics: Mechanisms of Drug Action

Once a drug has passed from the blood supply into the brain it can begin to exert its effects on neuronal functioning. A basic principle of **pharmacodynamics** is that drug effects are mediated by their influence on target cells. While many of these effects are

caused by the interaction between a drug and specific receptors, other effects may be mediated by a drug's effects on neurotransmitter synthesis, storage, release, reuptake, or on its metabolism. Ultimately all psychoactive drugs alter neural function by either facilitating or inhibiting neurotransmission. When a drug acts to facilitate neurotransmission it is called an **agonist** and when it acts to inhibit or decrease neurotransmission it is referred to as an **antagonist**.

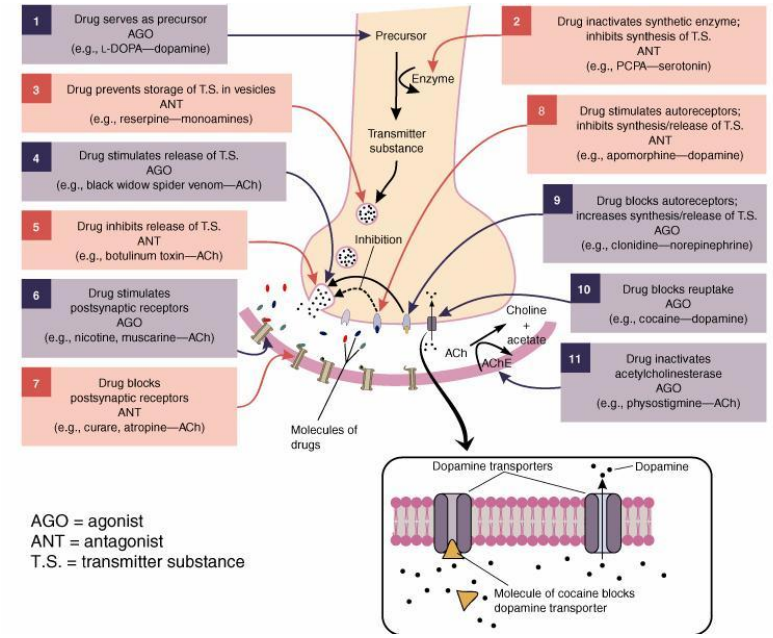

***Figure 13**: Mechanisms of Drug Action (Adapted from Carlson, 2010)*

Drug Agonists Because there is a long chain of events leading the synthesis, storage, release, and breakdown of neurotransmitter substances, there are numerous opportunities to alter these processes with drugs. Some of these drug effects are transient, lasting only as long as the drug is present. Other effects are longer term affecting receptor expression

and protein synthesis. We will examine some of the most common ways drugs act to facilitate neural communication. Drugs that directly bind to, and activate receptor sites are called direct agonists. Drugs that facilitate neurotransmission by increasing neurotransmitter availability or release are called indirect agonists.

Neurotransmitter synthesis and availability Some drugs function as agonists by either increasing the synthesis of a neurotransmitter or by increasing the amount released into the synapse. As you recall, neurotransmitters are synthesized from precursor compounds in the neurons that release them. Increasing the availability of precursor compounds and/or the rate limiting enzymes necessary for their production can increase neurotransmitter availability. For example, the dopamine agonist L-DOPA (3, 4-dihydroxy-L-phenylanine), which is commonly used to treat Parkinson's disease, is the metabolic precursor to dopamine. L-DOPA readily crosses the blood brain barrier, unlike dopamine, and is quickly converted into dopamine by the enzyme aromatic amino acid decarboxylase. Because this enzyme is also found in peripheral tissues some of the L-DOPA gets converted into dopamine before it reaches dopaminergic neurons. To prevent this from occurring peripheral inhibitors of aromatic amino acid decarboxylase such as Carbidopa are co administered with L-DOPA.

Neurotransmitter Release Neurotransmitter is typically released from synaptic vesicles directly into the synaptic gap only after they have fused with the presynaptic membrane. However, some drugs may actually enhance the amount of neurotransmitter released by causing it to be released into the presynaptic terminal where it is then transported into the synaptic gap. Amphetamine and methamphetamine are examples of dopamine agonists that increase dopamine activity by causing dopamine to leak from the synaptic vesicles

into the terminal button. Additionally these drugs cause the dopamine transporter to operate in reverse and carry this intracellular dopamine outside of the cell where it can activate dopamine receptors.

Although not a drug, the venom from black widow spiders, as well as some poisonous snakes, acts as an acetylcholine agonist by increasing the amount of ACh released into the synapse. This results in over activity of acetylcholine neurons at neuromuscular synapses causing muscular contraction. In humans black widow spider venom is rarely lethal, but the venom from snakes which is delivered in much larger quantities can be.

Neurotransmitter Breakdown and Reuptake The breakdown and reuptake processes that terminate the activity of neurotransmitter released into the synapse are essential for normal neuronal activity. These processes, however, may also be altered by drug action resulting in prolonged neurotransmitter activity. The catecholamine neurotransmitters dopamine and norepinephrine as well as the monoamine serotonin are degraded by the synaptic enzyme monoamine oxidase (MAO). Drugs that block the activity of this enzyme, called MAO inhibitors (MAOIs), enhance neural activity preventing the metabolic breakdown of these neurotransmitters. Because all three of these neurotransmitters are degraded by MAO, MAO inhibitors are not selective in agonizing any one of them specifically. MAO inhibitors such as phenelzine (Nardil) are used as antidepressants and will be discussed later on.

Blocking the **reuptake** of intact neurotransmitter is an effective way to enhance neurotransmission either selectively or in combination with other neurotransmitters. Blocking reuptake prolongs the action of neurotransmitters on their receptors. This has

the immediate effect of increasing neurotransmission and a delayed effect of prompting downregulation of the receptors. The popular antidepressant fluoxetine (Prozac) acts as a **selective serotonin reuptake inhibitor** (SSRI) by blocking the serotonin transporter. Several new generation antidepressants act to inhibit the reuptake of both serotonin and norepinephrine. These drugs may be as effective as the SSRIs without some of the adverse side effects.

Neurotransmitter Receptor Activation Some drugs, because of their chemical structure, actually bind selectively with specific receptors and agonize neurotransmission directly (direct agonist). In these cases the drug is said to have a high binding affinity for the receptor. Occasionally a drug has such high affinity it competes effectively with the natural ligand or neurotransmitter for these receptors. Because there are no reuptake transporters for drugs, and they are not degraded by synaptic enzymes quickly, these drugs may have prolonged effects. The hallucinogenic drug lysergic acid diethylamide (LSD) is an example of such a drug. LSD has a high affinity for most serotonin receptors but its hallucinogenic effects are believed to be mediated by the 5-HT_2 subtype. Other hallucinogenic drugs have similar agonistic actions on serotonin receptors.

Drug	Mechanism of Action
Cocaine	Dopamine Agonist
L-DOPA	Dopamine Agonist
Amphetamine	Dopamine/Norepinephrine Agonist
Prozac	Serotonin Agonist
Valium	GABA Agonist
Alcohol	GABA Agonist
Thorazine	Dopamine Antagonist
Atropine	Acetylcholine Antagonist
Marijuana	Cannabinoid Agonist
LSD	Serotonin Agonist
Narcan	Opiate Antagonist

Table 3*: Common drugs that act as agonists and antagonists*

Drug Antagonists

If a heroin overdose victim suffering from respiratory and cardiac failure is fortunate enough to make it to an emergency room they will likely receive an intravenous injection of naloxone (Narcan). Within a minute respiration and heart function will return to normal and the patient will again be responsive to pain and to his surroundings. Without the injection of this powerful opiate antagonist this patient may not have survived. Drug antagonists function to inhibit or block neurotransmission. In this example naloxone competes for the same opiate receptors as heroin, but even more effectively. The difference is that naloxone does not activate the receptor, it merely blocks it so neither heroin nor the endogenous ligand (an endorphin) can exert its effects. Within a few hours naloxone is metabolized and excreted and opiate receptors may return to normal. Not all antagonists work this directly on receptors. As we saw with drug

agonists there are many steps in the neurotransmission process and drugs can antagonize them all.

Neurotransmitter Synthesis and Availability The synthesis of catecholamine neurotransmitters is dependent upon the availability of both dietary tyrosine and the enzyme tyrosine hydroxylase which converts it into DOPA. The drug α-methyl-para-tyrosine (AMPT) acts as an indirect antagonist by blocking the ability of tyrosine hydroxylase to catalyze this conversion, thus depleting both dopamine and norepinephrine. In animals studies this depletion causes behavioral depression and movement disorders. In humans AMPT has been used to treat dyskinesia, a movement disorder, and has been shown to induce relapse of major depression and seasonal affective disorder—a type of depression associated with low levels of ambient light.

Neurotransmitter availability can also be disrupted by drug. For example, the antihypertensive drug reserpine binds to the vesicular transporter protein preventing newly synthesized or recycled catecholamines and serotonin from being transported into synaptic vesicles. As you may recall from earlier on neurotransmitter remaining in the terminal button is quickly degraded by MAO. Reserpine nonselectively antagonizes dopamine, norepinephrine and serotonin by depletion, producing behavioral depression and sedation. Because of these central effects, reserpine is only rarely used to treat hypertension today. Reserpine is used in animal studies that are investigating the roles of catecholamine and serotonin depletion in depression.

Neurotransmitter Release The release of catecholamine neurotransmitters is regulated by presynaptic autoreceptors. The receptor subtypes of these autoreceptors are the α_2 receptor for norepinephrine and the D_2 receptor for dopamine. Drugs that stimulate these receptors actually reduce the amount of neurotransmitter released. Because very few drugs have affinities for specific subtypes of receptors, the effects of drugs can be contradictory. That is, a drug such as apomorphine (derived from morphine) stimulates dopamine receptors, but because it agonizes D_2 receptors it actually decreases dopamine release from neurons containing them. So, apomorphine, although a dopamine agonist, has antagonistic effects on some dopamine neurons.

Botulism toxin is another example of a substance that inhibits the release of neurotransmitter. In this case it antagonizes acetylcholine by preventing synaptic vesicles from fusing with the presynaptic membrane. The effect of poisoning is muscle weakness and in severe cases botulism toxin can cause asphyxiation and death. In extremely small doses botulism toxin (Botox) is used as a cosmetic to eliminate facial wrinkles. It does this by paralyzing small groups of muscle cells that, in their contracted state, cause wrinkles.

Neurotransmitter Receptor Activation In the early 1950s, well before the catecholamine neurotransmitters were identified, the drug chlorpromazine (Thorazine) was introduced as the first drug to treat schizophrenia which is perhaps the most debilitating of all of the psychological disorders. While chlorpromazine was rapidly becoming the treatment of choice for severe psychosis, its mechanism of action remained a mystery for nearly a decade. We now know that chlorpromazine acts as a direct antagonist on dopamine

receptors. This discovery has led to modern theories describing the molecular basis of schizophrenia as well as to many new drugs for its treatment. By blocking dopamine receptors, chlorpromazine disrupts dopamine neurotransmission in the basal ganglia, the mesolimbic system, and in the cortex.

Drugs that directly antagonize receptors vary in their affinity for specific receptor subtypes. Newer drugs being developed for schizophrenia treatment are focused on minimizing the severe motor side effects associated with older medications by targeting specific dopamine receptors. We will examine this in more detail in the chapter on antipsychotic medication.

In this section we have reviewed examples of how drugs can act to both facilitate and disrupt neurotransmission. Because there are many steps in the neurotransmission process there are many ways to alter neural activity with drugs. Using drugs to alter neurotransmission has led to a greater understanding of just how different neurotransmitter systems contribute to both normal and disordered behavior. It has also led to far more effective treatment for behavior disorders while at the same time minimizing troubling side effects.

As we will see in the following chapters, modern drug development is going beyond altering drug-receptor interactions and examining ways to alter the expression of genes within specific populations of neurons. These manipulations can affect receptor expression as well and other properties of cell functioning that may contribute to the treatment of psychological disorders.

Chapter 2: Glossary of terms in bold

pharmacokinetics the science of how drugs are absorbed, distributed to body tissues, and eliminated from the body after metabolism.

pharmacodynamics the science of the mechanisms of drug action or how drugs affect target cells and induce pharmacological effects.

blood brain barrier (or BBB) a relatively impermeable membrane forming and surrounding capillaries in the brain that prevents most substances from leaving the circulatory system and entering the brain.

depot binding drug binding to inactive sites.

half-life the amount of time it takes for a drug's blood level to be decreased by metabolism and elimination by 50% (1/2 of its peak blood level).

dose response curve the relationship between a drug dose and it physiological effects. Often this relationship is sigmoidal.

respiratory depression a decrease in respiratory depth and frequency caused by inhibition of respiratory centers in the brain stem. Often the cause of death from drug or alcohol overdose.

tolerance a decrease in the effectiveness of a drug after repeated administration. This is observed as a shift to the right in the dose response curve.

cross-tolerance tolerance to a drug in the same class as the drug administered repeatedly. Tolerance may be observed to codeine after it has already developed to morphine.

metabolic tolerance metabolic enzymes that break drugs into water soluble compounds actually increase in availability after repeated exposure to a drug. This results in more rapid metabolism as more enzymes are available for degradation.

cellular tolerance cellular adaptations to some drugs that diminish their effects on target cells.

associative tolerance a decrease in responsiveness to drugs that is controlled by cues associated with drug use and onset. Conditioned tolerance is a consequence of Pavlovian conditioning.

behavioral tolerance learned behavioral adaptations that occur in a drug state and contribute to enhanced motor performance. Also referred to as state-dependent learning.

downregulation a decrease in neurotransmitter synthesis or release caused by drug action on target receptors. Downregulation may also involve decreases in receptor availability.

therapeutic index the range between a drug's therapeutically effective dose and its lethal or toxic dose. The therapeutic index can decrease as tolerance develops.

placebo a pharmacologically inert substance administered under the guise of medication.

double-blind in a double blind experiment neither the patients nor the physician know which patient group receives the placebo or the actual medication. This experimental design can eliminate both subject and researcher biases which may affect the outcome of drug trials.

agonist a substance that facilitates or increases neural transmission.

antagonist a substance that inhibits or decreases neural transmission.

reuptake a process where neurotransmitter substances are removed from the synaptic gap and returned to the terminal button of the transmitting neuron. Reuptake decreases the availability of the neurotransmitter at receptor sites.

selective serotonin reuptake inhibitor a class of antidepressant drugs that selectively inhibit serotonin reuptake leaving serotonin available at receptor sites.

chemical name a drug's chemical name reveals its chemical composition and molecular structure.

brand name a drug's brand or trade name is a name given by its manufacture and is used in advertising the drug. A drug brand name is protected by a patent

generic drug generic drugs must contain the same active ingredients as the original brand name drug and they must be pharmacologically equivalent. Because several manufactures may compete to produce and market generic drugs their cost is often considerably less than their equivalent brand named drug