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How Methadone Works

by

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The Pharmacology of Methadone

Ignorance about methadone abounds. Professionals working in the field receive very little or no training at all about the very medication that they will be administering. Rarely is addiction viewed as a disease and under the domain of the medical profession. Even the medical profession does not understand addiction, and most physicians, nurses or other medical professionals receive very little training about addiction. Their education regarding methadone is usually on its use in withdrawing an individual from opiates while its best property- that of maintenance, is neglected. Counselors, social workers and psychologists know even less than the medical professions. They usually receive very little education in basic science and even less about the biology of behavior, or the functioning of the brain. Thus, both medical and counseling professionals have been taught to approach addiction as a character disorder and administer methadone as a substitute.

With such a deficiency within higher education added to the public's misunderstanding about addiction it is not surprising that myths about methadone thrive. Of course, there is an additional reason why there is so much misinformation about methadone, and that is because methadone is the only effective treatment for heroin addiction. Since the introduction of methadone maintenance treatment it has been attacked by abstinence oriented modalities attempting to denigrate methadone and therefore improve their chances for funding. Prior to methadone treatment the only form of treatment for heroin addiction was the abstinence oriented modalities i.e., Project Return, Phoenix House. Abstinence oriented modalities controlled most state regulating agencies and many still do. Only New York State, which has a large methadone system that treats about one-fifth of all methadone patients in the United States has a state agency that is supportive of methadone.

With such misunderstanding about methadone the only way for methadone patients to deal with it and to insure adequate health care and supportive services is to educate themselves. In this way methadone patients can educate others about heroin addiction and methadone treatment. That is the purpose of this paper and although some of the topics are very technical it is not important that you understand every word. Instead try to get just a basic understanding of everything.

The next time you hear something "crazy" about methadone ask that person for the scientific proof. Ask for references and publications. You will discover that usually they have none, instead relying on the "everybody knows" method of science!

Basics of Pharmacology

Pharmacology is the study (ology) of drugs (pharmac/y) and psychopharmacology is the study of (ology) drugs (pharmacolog/y) that produce their effects on the mind or brain (psycho or psyche). There are five basic classes of psycho-active drugs: 1) the opioids (heroin and methadone), 2) the stimulants (cocaine, nicotine), 3) the depressants (tranquilizers, antipsychotics, alcohol), 4) hallucinogens (LSD), and 5) marijuana and hashish.

Most compounds, including opioids exist in two forms distinguished by levo or dextro preceding the compound (i.e., levo-methadone, dextro-methadone). One form is active and one inactive. Generally speaking the active form is usually the levo form and very often levo is dropped from the compounds name. The best way to think of these two forms is your two hands. Both the right and left hand have the same structures (i.e., one thumb and four fingers) but they are mirror images of one another. And like hands, the levo and dextro form are very different from one another, yet similar.

Administration

An important factor in how a psychoactive drug exerts it effects is how it is administered. Administration refers to the mechanisms by which drugs are transmported from the point of entry into the bloodstream. Drugs are commonly administered in five ways: 1) orally, 2) rectally, 3) parenterally (injection), 4) the membranes of the mouth or nose, and 5) by inhalation. Each method of administration has its advantages and disadvantages.

- **Oral**
  Easiest method of administration. Disadvantages include the possibility of vomiting, the differing rates of absorbtion from person to person, and the fact that some drugs are not absorbed well.
- **Rectal**
  Easy administration, especially for children. Disadvantage is that rectal absorbtion is often irregular.
- **Pulmonary** (through the lungs)
  Very little is known about the pulmonary absorbtion of drugs other than those administered as gases.
- **Intravenous injection**
  Avoids all the disadvantages of oral administration. More control of dosage is possible and the drug is placed in circulation with minimal delay. Also most dangerous means because of rapidity of onset. Allergic reactions that are mild when drugs are administered orally may be severe when administration is intravenous.
- **Intramuscular injection**
  Same as intravenous.
- **Subcutaneous injection**
  Same as intravenous. Irritating drugs should be avoided.

After a drug is administered the next important determinant in the drugs ability to exert its effect is how the drug is distributed throughout the body. Once the drug reaches the bloodstream it is distributed throughout the body. However, it must be able to pass across various barriers in order to reach the site of action. Only a very small portion of the total amount of a drug in the body at any one time is in direct contact with the specific cells that produce the pharmacological effect of the drug. Most of the drug is found in areas of body that are remote from the drug's site of action. In the case of psychoactive drugs, most of the drug is to

be found outside of the brain and is therfore not directly contributing to the psychopharmacological effect.

Four types of membranes are most important in drug distribution:

1. Cell walls
2. Walls of capillary vessels of the circulatory system
3. The blood-brain barrier
4. The placental barrier

Cell Membranes: In order to be absorbed from the intestine or gain access to the interior of a cell, a drug must be able to penetrate the cell membranes. The characteristic feature of cell membranes are fat molecules coated by a protein layer on each surface. Like a bimolecular sandwich the fat molecules (cheese) are sandwiched between two layers of protein (the bread). Only drugs that are soluble in fat are permeable and can pass through the cell membrane. The cell membrane also contains small pores that allow water-soluble molecules to pass through. Most drugs are too large to pass through the pores and, thus, most water-soluble, fat-insoluble drugs cannot pass through the cellular barrier.

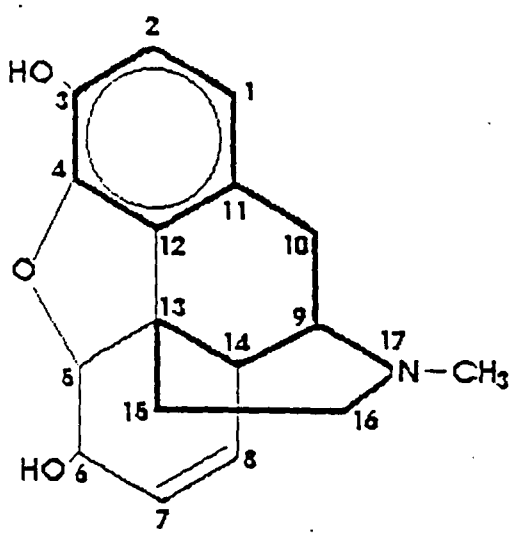
Blood Capillaries: Within a minute or so of a drug entering the bloodstream, it is distributed farily evenly through the bloodstream. However, most drugs are not confined to the bloodstream and are readily exchanged back and forth across the blood capillaries. The capillary walls contain pores that are large enough for most drugs to pass through, therefore it does not matter whether a drug is fat-soluble or insoluble for it to pass through capillary walls.

Blood-Brain Barrier: For drugs to enter the central nervous system they must be able to penetrate the Blood-Brain Barrier (BBB). The BBB decreases the permeability of the capillary membranes thus protecting the brain from various substances that would otherwise be harmful. Capillaries of the brain are tightly joined and covered by a footlike sheaf structure that arises from a nearby cell called an astrocyte. To enter the brain, drugs must traverse not only the capillary wall but also the membranes of the astrocytes in order to reach their target cells.

Placential Barrier: Among all the membrane systems of the body, the placenta is unique: it separates two distinct human beings with differing genetic compositions, physiological resonses, and sensitivities to drugs. The fetus obtains essential nutrients and eliminates.metabolic waste products through the placenta without depending on its own organs, many of which are not yet functioning. This dependnece of the fetus on the mother places it at the mercy of the placenta when foreign substances appear in the mother's blood.

The Opioids

All natural and synthetic opioids exhibit a three dimensional T-shaped configuration (Barchas, Berger, Ciaranello and Elliott, 1977). This T-shaped molecule has two broad hydrophobic surfaces which are at right angles and a methylated nitrogen which is usually charged at physiological pH. The charged nitrogen is essential for activity and lies in one of the hydrophobic planes. A hydroxyl group at carbon 3 on the other plane is also essential. This configuration which all opioids have is called the piperidine ring. Figure 1 is the structure of morphine with the piperidine ring indicated by bold lines.



Endogenous Opioids

The term endorphin is used to characterize a group of endogenous peptides whose pharmacological action mimics that of opium and its analogs. The endogenous opioid system is complex with a multiplicity of functions within any given organism. There exists about two dozen known endogenous opioids which belong to one of three endogenous opioid systems: 1) the endorphin system, 2) the enkephalin interneuron system, and 3) the dynorphin system.

The endogenous opioid system may play a role in a wide variety functions such as, the production of analgesia, attention, memory, catatonia, schizophrenia, manic depression, immune function, endocrine function, appetite regulation, sexual behavior, postpartum depression, release of several hormones, locomotor activity, anticonvulsant activity, body temperature regulation, meiosis (pin point pupils), shock, respiration, sleep and drug dependence.

Endorphins are peptides which are biologically active substances in the brain composed of amino acids that are produced in neurons. Today peptides are considered to be a distinct and separate group of psychoactive substances in the brain.

The Target of Action: The Receptor

Most psychoactive drugs exert their action at a receptor. This can be through of as a "lock and key" with the key as the drug opening the lock, or receptor. Opiate receptors can be broken down further into types: the m receptor prefers morphine, heroin and methadone, the e receptor prefers b-endorphin, the d receptor prefers enkephalins, and the k receptor that prefers dynorphins. Some receptors are broken down further into subtypes as in the k1 and k2 receptors. A substance that binds to a receptor is called a ligand, thus endorphins are the natural ligand for the opiate receptor. The entire endogenous opioid system is referred to as the "Endogenous Opiate Receptor Ligand System."

Receptors have several properties. Any substance, including the endogenous ligand or any exogenous compound that attaches to a receptor occurs through a process of chemical bonding. This is referred to as binding to a receptor. Affinity refers to the strength that a substance binds to a receptor. Some chemical

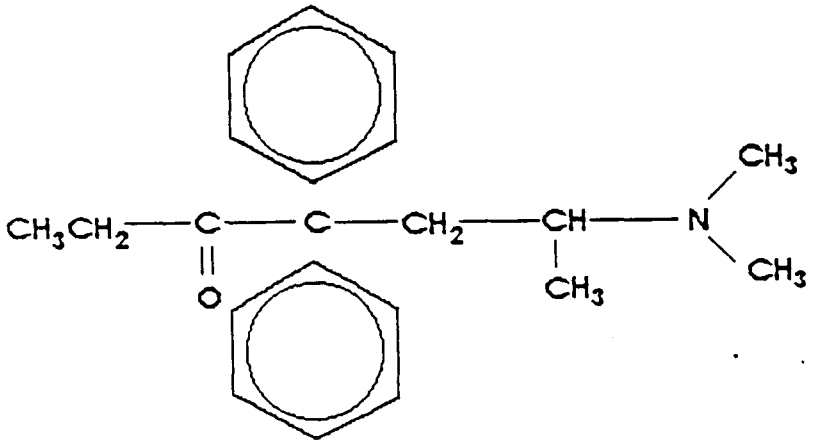
bonds are stronger than others resulting in some substances having a greater affinity than others for a receptor. In respect to opiate receptors and opioid analgesics the stronger the affinity, the stronger the analgesic properties of the substance. Therefore, morphine which is a strong analgesic has a stronger affinity for the opiate receptor than codeine which is a weaker analgesic.

Opiate receptors have been found in every vertebrate and even in some invertebrate species. Therefore, opiate receptors and the endogenous opioids are basic within the scheme of evolution. Their vast distribution in species implies that endorphins were important in mammalian evolution.

Methadone and Congeners

Methadone was synthesized by German chemists during Wold War II when the United States and our allies cut off their opium supply. And it is difficult to fight a war without analgesics so the Germans went to work and synthesized a number of medications in use today, including demerol and darvon which is structurally simular to methadone. And before we go further lets clear up another myth. Methadone, or dolophine was not named after Adolf Hitler. The "dol" in dolophine comes from the latin root "dolor." The female name Dolores is derived from it and the term dol is used in pain research to measure pain e.g., one dol is 1 unit of pain.

Even methadone, which looks strikingly different from other opioid agonists, has steric forces which produce a configuration that closely resembles that of other opiates (Figure 2). Anotherwords, steric forces bend the molecule of methadone into the correct configuration to fit into the opiate receptor.

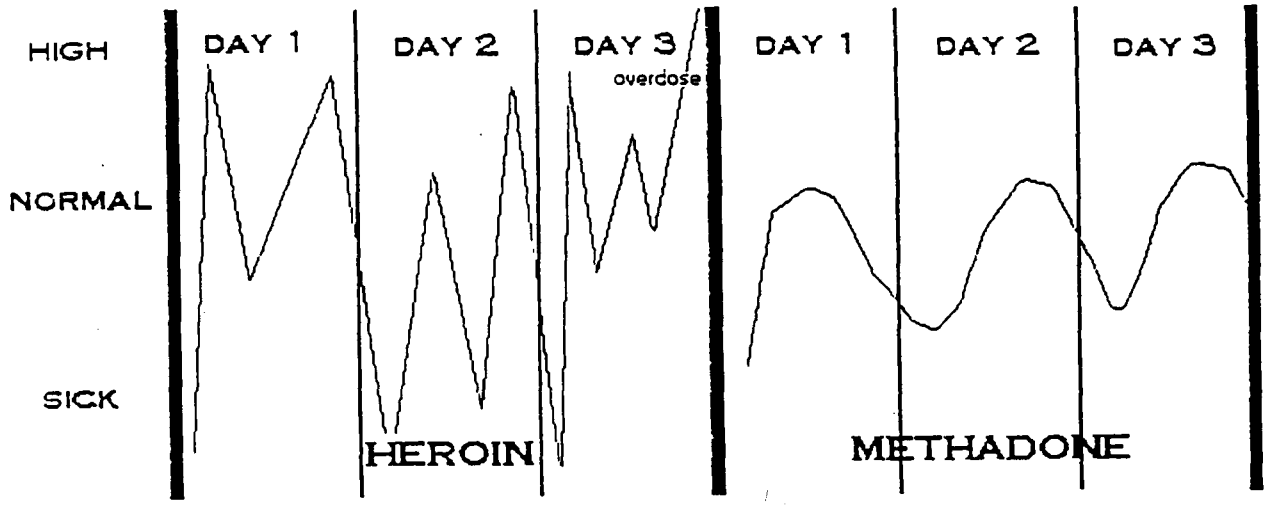


An agonist is a substance that binds to the receptor and produces a response that is similar in effect to the natural ligand. In contrast, antagonists bind to the receptor but block it by not allowing the natural ligand or any other compound to bind to the receptor. Antagonists do not cause the opposite effect. They merely fit into the receptor and block any other substance from binding to it. For example, narcotic antagonists such as naloxone or its' predecessor naline are administered to reverse a heroin or opioid overdose. This is achieved because opioid antagonists have a greater affinity for the opiate receptor than agonists and in fact the affinity is so strong that narcotic antagonists can literally knock an agonist right out of the receptor. The effect is very fast and the overdose victim will wake up within minutes, or seconds even. Individuals dependent on heroin, or other opioids such as methadone can wake up in withdrawal.

Heroin, methadone and morphine are opioid agonists. Narcotic antagonists are produced by a change on the nitrogen atom of an opioid agonist. Thus nalorphine is produced from a change in the nitrogen atom of the morphine molecule and naloxone is produced from oxymorphone. Naltrexone is a long acting narcotic antagonist which is used for maintenance treatment. It works by binding to the receptor over a 24 hour period thus making any injection or administration of an opioid agonist ineffective. It must be emphasized that naltrexone does not have agonist properties it merely blocks every opiate receptor irrespective of that receptors function. Thus, long term treatment with narcotic antagonists can also block important biological functions and various side effects have been reported, including hypersexuality.

How Methadone Works Its Miracle

When you take methadone it first must be metabolized in the liver to a product that your body can use. Excess methadone is also stored in the liver and blood stream and this is how methadone works its 'time release trick' and last for 24 hours or more (Inturrisi and Verebey, 1972). The higher the dose the more that is stored. This is why patients on blockade doses (70 mg/day or more) are able to go for a day or two without their medication. Of course the down side to this is that when a patient misses a dose they will begin to "destabilize" which places them at risk of overdose should they attempt to administer heroin. They are slowly loosing the blockade effect of methadone and may begin to experience drug hunger and craving.



Once in the blood stream metabolized methadone is slowly passed to the brain when it is needed to fill opiate receptors. In no way do vitamins interfere with the binding of methadone to the opiate receptor where methadone mimics the endorphins. No other medication has received the scrutiny and evaluations that methadone has which continue to this day (over thirty years) (Ball and Ross, 1991; Brecher, 1972; Caplehorn, 1994; Cooper, 1992; Dole, 1988; Dole and Joseph, 1978; Dole and Nyswander, 1965; GAO, 1990; Gearing and Schweitzer, 1974; Joseph and Dole, 1970; Kreek, 1978 and 1973; Zweben and Payte, 1990). Methadone is perhaps one of the safest drugs known and only a few side effects which usually subside after stabilization and the first year of treatment. I know of no one who is allergic to methadone.

Drugs and Conditions that Reduce the Action of Methadone

Narcotic Antagonists and Agonist-Antagonists Drugs

An important property of all narcotic antagonists is that anyone dependent on any opiate, including methadone patients will be extremely sensitive to them. These actions occur directly at the opiate receptor in the brain. Some of the new analgesics are mixed agonist-antagonists drugs which have been developed to reduce their addiction potential. For a non dependent person these medications are pain killers, however for methadone patients, or anyone dependent on opioids their use is contra indicated because the individual will be thrown into withdrawal. Talwin which is noted on the identification cards for methadone patients is the most commonly used mixed agonist-antagonist analgesic. Other common mixed agonist-antagonist opioids used in obstetrics are Nubain and Stadol.

Drugs and Conditions That Impact on Metabolism

It is estimated that about 5% of methadone patients are what is called aberrant metabolizers (Payte and Khuri, 1992). Metabolism is necessary for methadone to be converted into a metabolite that the body can use. A damaged liver can fail to metabolize enough methadone for storage and the result is that unmetabolized methadone is excreted. The result is that the body is unable to use the methadone and the patient will begin to experience abstinence symptoms (withdrawal). Liver disease and alcoholism can cause a reduction of the liver's ability to perform normal metabolic functions, including the metabolism of methadone to a produce that your body can use. This condition is very difficult to correct and the only way to help the liver would be to eat a low fat diet to allow the liver to rest while increasing the dosage of methadone. However, it is almost impossible to keep an alcoholic methadone patient approaching liver failure and eventual death comfortable and free of abstinence symptoms.

Various drugs can cause the liver to speed up metabolism. When this occurs most of the methadone is excreted before it can be converted to a metabolite that the body can use. Drugs that cause an increase in metabolism are rifampin for tuberculosis (Tong et al, 1981), dilantin for epilepsy (Kreek, Gutjahr, Garfield, Bowen and Field, 1976). Carbamazepine can speed up the metabolism of methadone so that it is excreted unused (Payte and Khuri, 1992). The easiest way to correct the problem is to raise the dose and/or break the dose down into several doses throughout a 24 hour period (Payte and Khuri, 1992). For example, a patient on 120 mgs/day might break their dose into thirds taking one third in the morning, one third at dinner time and one third before going to bed. In a sense this helps to regulate the liver's metabolism. Unfortunately, most programs do not utilize this later procedure because it is more difficult than just raising the dose until the patient stops experiencing symptoms of abstinence.

Cocaine Use and Opiate Receptors

A recent discovery is that cocaine use can cause an increase in the number of brain opiate receptors. Brain receptors are not static, rather they are compounds floating along the surface of the membrane. The number of receptors for any natural ligand can change dependent of various conditions. As expected an increase in the number of opiate receptors would reduce the action of methadone. For example, lets say a patient is on 100 mgs/day. Lets use small round numbers to demonstrate this, normally there are hundreds of thousands of oiate receptors in the human brain, but for this example when the patient is on a stable dose the number of opiate receptors in the brain averages around 100. And 75 percent of the 100 opiate receptors, or 75 remained filled throughout a 24 hour period. Now this patient begins to use cocaine which causes an increase in the number of opiate receptors to 150. However, only 75 receptors remain filled and active and instead of 75 percent of the receptors being filled now only 50 percent are filled. The patient complains that the cocaine is eating up their methadone and asks for a raise. And probably the patient will need their dose to be increased for 20-30 mgs/day to feel the same.

Barbiturates

There has been one or two reports of a barbiturate causing abstinence in a methadone patient. While this is a rare occurance and the causes have not been determined all methadone patients should be aware of it.

The Myth of Vitamin C

A recent myth has surfaced about vitamin C impacting on methadone. And as usual no data, or at least scientific data are given. If Vitamin C did interfere with methadone it would have been discovered years ago when methadone was administered in orange juice. Vitamin C does not enter the brain and even if it did it could not compete with methadone for opiate receptors because it does not contain the right chemical machinery, namely the piperidine ring (Figure 3). To fit into the opiate receptor a molecule must have the proper chemical configuration. Vitamin C has no relation to the opiate structure and therefore cannot interfere with the process of binding to the receptor. In fact Vitamin C has very little to do with neurological functioning. The primary functions of Vitamin C are to promote metabolic reactions, in particular protein metabolism and is important in the laying down of collagen during connective tissue formation. Methadone is not a protein or involved in connective tissue formation. The molecular structure of the two are in no way related and therefore have nothing to do with one another.

Nor would vitamin C impact on methadone metabolism because it does not cause metabolism to increase or decrease. The main impact that vitamin C has is to provide necessary vitamins that many patients do not get in their diet. All the vitamin C myth does is to cause fear, apprehension and raise suspictions about methadone. Whoever has promoted this myth is anti-methadone and therefore anti-methadone patient. Why? Because when methadone patients are firghtened and suspicious of the very medication that has saved their lives they can not concentrate on the important tasks at hand -- that of changing their lives!

Where To Get Information

Pharmacological information about methadone and other psychoactive drugs can be found in The Pharmacologists Bible, or Goodman and Gillman's The Pharmacological Basis of Therapeutics. Goodman and Gillman is far superior to the reference book, The Physician's Desk Reference (PDR) that most go to for information because it gives not only clinical information as the PDR, but pharmacology, metabolism and the recent research findings.

NAMA produces an Education Series and provides scientific publications. Another source is the National Clearinghouse for Alcohol and Drug Information (1-800-SAY-NO-TO(DRUGS)) that will do a literature search and send either a bibliography for you to chose from or send publications directly. Sometimes the later choice cannot be done because of the vast amount of literature.

So beware of myth-makers and "everybody knows science." Methadone is one of the safest and most effective procedures that I know of, yet it is constantly denigrated by nay sayers who do not understand methadone maintenance or heroin addiction. Challenge the nay sayers! Ask them for proof, real science!

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